# Dopamine and Oculomotor Impulsivity In Health & Disease

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**I, Robert James Adam confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.**

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# Publications

Peer reviewed publications resulting from work presented in this thesis:

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Adam, R., Leff, A., Sinha, N., Turner, C., Bays, P., Draganski, B., and Husain, M. (2013). Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. Cortex J. Devoted Study Nerv. Syst. Behav. 49, 1292–1303.

*...You have brains in your head.*
*You have feet in your shoes*
*You can steer yourself*
*any direction you choose.*
*You're on your own. And you know what you know.*
*And YOU are the guy who'll decide where to go.*

*...You won't lag behind, because you'll have the speed.*
*You'll pass the whole gang and you'll soon take the lead.*
*Wherever you fly, you'll be the best of the best.*
*Wherever you go, you will top all the rest.*

*...You will come to a place where the streets are not marked.*
*Some windows are lighted. But mostly they're darked.*
*A place you could sprain both you elbow and chin!*
*Do you dare to stay out? Do you dare to go in?*
*How much can you lose? How much can you win?*

*And IF you go in, should you turn left or right...*
*or right-and-three-quarters? Or, maybe, not quite?*
*Or go around back and sneak in from behind?*
*Simple it's not, I'm afraid you will find,*
*for a mind-maker-upper to make up his mind.*

*You can get so confused*
*that you'll start in to race*
*down long wiggled roads at a break-necking pace*
*and grind on for miles across weirdish wild space,*
*headed, I fear, toward a most useless place.*
*The Waiting Place...*

*...for people just waiting.*
*Waiting for a train to go*
*or a bus to come, or a plane to go*
*or the mail to come, or the rain to go*
*or the phone to ring, or the snow to snow*
*or waiting around for a Yes or a No*
*or waiting for their hair to grow.*
*Everyone is just waiting.*

*Oh, the places you'll go! There is fun to be done!*
*There are points to be scored. there are games to be won.*
*And the magical things you can do with that ball*
*will make you the winning-est winner of all.*

Exerpts from “Oh, The Places You’ll Go!” (Dr. Seuss, 1990)

# Abstract

The role of subcortical pathology in altered cognition is increasingly recognised. However, measurement and monitoring of impairments in motivation and behaviour due to subcortical disease is challenging. Basal ganglia – cortico-thalamo-cortical loops and the neurotransmitter, dopamine, are recognised to be important in modulating both reward learning and oculomotor performance. This thesis considers the use of novel and adapted oculomotor (saccadic) tasks as a means of interrogating these dynamic circuits as measures of rewarded decision-making under risk and time pressure.

I first describe a novel rewarded oculomotor task, the Traffic Light Task, which provokes two distributions of saccades – one anticipatory, and one reactive. The balance of these distributions, the number of errors and the reward obtained are used to index oculomotor decision-making. Demonstrated effects of healthy aging include a significant reduction in anticipatory responding and consequent reduction in reward. I then compare behavioural oculomotor task responses in healthy controls with established "self-report" measures of impulsivity, finding significant correlations. Next, I consider a patient with focal lesions of the basal ganglia causing profound apathy. I demonstrate reduced oculomotor anticipatory responding and reward sensitivity. I then show the positive effects of dopaminergic medications (levodopa and ropinirole) upon his oculomotor decision-making in tandem with a clinical improvement in his motivational state. To further qualify this dopaminergic effect, I then assess the effects of two dopaminergic drugs (levodopa and methylphenidate) upon healthy volunteers. Finally, I use oculomotor tasks to compare patients with Parkinson's Disease, with and without impulse control disorders, with both healthy volunteers and pathological gamblers without neurological disease.

The results of these experiments raise questions regarding the development of models of basal ganglia – cortico-thalamo-cortical loops and how best to understand them.

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# Abbreviations

| | | |
|---|---|---|
| ACC | - | Anterior Cingulate Cortex |
| ADHD | - | Attention Deficit Hyperactivity Disorder |
| AER | - | Anticipations : Errors Ratio |
| AI | - | Attentional Impulsiveness (BIS-11 Second Order Factor) |
| ANOVA | - | Analysis of Variance |
| BART | - | Balloon Analog Risk taking Task |
| BOLD | - | Blood Oxygen Level Dependent |
| BIS-11 | - | Barratt Impulsiveness Scale (Version 11) |
| CBGTC | - | Cortico-basal ganglia-thalamo-cortical loop(s) |
| CGT | - | Cambridge Gambling Task |
| CSF | - | Cerebrospinal Fluid |
| DA | - | Dopamine |
| DAg | - | Dopamine Agonist |
| DaT | - | Dopamine Transporter |
| DBS | - | Deep Brain Stimulation |
| DLPFC | - | Dorsolateral Prefrontal Cortex |
| DR | - | Dopamine receptor {D1,D2,D3} |
| EMG | - | Electromyography |
| FEF | - | Frontal Eye Fields |
| fMRI | - | Functional Magnetic Resonance Imaging |
| GABA | - | Gamma Amino Butyric Acid |
| GDT | - | Game of Dice Task |
| GP | - | Globus Pallidus (GPi, .. Interna; GPe .. Externa) |
| HA | - | Harm Avoidance (Cloninger TPQ Dimension) |
| ICD | - | Impulse Control Disorder |
| IGT | - | Iowa Gambling Task |
| L-dopa | - | Levodopa, L-dihydroxyphenylalanine |
| LATER | - | Linear Approach to Threshold with Ergodic Rate |
| LED | - | Light Emitting Diode |
| Lh | - | Lateral Habenula |
| LIP | - | Lateral Intraparietal Area |
| LOFC | - | Lateral Orbitofrontal Cortex |
| MGS | - | Memory Guided Saccades |
| MI | - | Motor Impulsiveness (BIS-11 Second Order Factor) |
| MLE | - | Maximum Likelihood Estimation |
| MPH | - | Methylphenidate |
| MNI | - | Montreal Neurological Institute |
| MRI | - | Magnetic Resonance Imaging |
| NA | - | Noradrenaline / Noradrenergic / Norepinephrine |
| NPI | - | Non-planning Impulsiveness (BIS-11 Second Order Factor) |
| NS | - | Novelty Seeking (Cloninger TPQ Dimension) |
| OFC | - | Orbitofrontal Cortex |
| PD | - | Parkinson's Disease |
| PET | - | Positron Emission Tomography |
| PFC | - | Prefrontal Cortex |
| RD | - | Reward Dependence (Cloninger TPQ Dimension) |
| ROI | - | Region of Interest |
| RT | - | Reaction Time |
| SAI | - | Stop Anticipation Interval |
| SD | - | Standard Deviation |
| SEF | - | Supplementary Eye Fields |
| SEM | - | Standard Error of the Mean |
| SNc | - | Substantia Nigra Pars Compacta |
| SNRI | - | Selective Noradrenaline Reuptake Inhibitor |
| SPECT | - | Single Photon Emission Computed Tomography |
| SPL | - | Superior Parietal Lobule |
| SRT | - | Saccadic Reaction Time |
| SSRT | - | Stop Signal Reaction Time |
| STN | - | Subthalamic Nucleus |
| TLT | - | Traffic Light Task |
| TPQ | - | Cloninger Tridimensional Personality Questionnaire |
| VLPFC | - | Ventrolateral Prefrontal Cortex |

# 1. Introduction

# 1.1 General Introduction

## 1.1.1. Basal ganglia thalamocortical loops and behaviour

Why do patients with basal ganglia pathology develop problems with motivation and behaviour? Diseases of subcortical areas, such as Parkinson's Disease (PD), have previously been oversimplified as "motor" disorders (Chaudhuri et al., 2006; Chaudhuri and Schapira, 2009; Weintraub and Burn, 2011; Burn et al., 2014) despite longstanding acknowledgment of the 'bradyphrenia' or slowness of thought and cognitive changes associated with the disease (Cools et al., 1984; Cummings JL and Benson D, 1984; Rafal et al., 1984). However, the important contributions of these areas to behaviour are now increasingly recognised (Dubois and Pillon, 1996; Middleton and Strick, 2000; Bonelli and Cummings, 2007, 2008; Koziol and Budding, 2009). There is a great deal of interest in deficits of motivation and decision-making due to PD and other conditions affecting the basal ganglia, partly due to the recognition of impulse disorders as a complication of the disease and/or its treatment (Weintraub and Nirenberg, 2012).

How might we predict which patients will develop such problems? Despite a better understanding of the dynamic mechanisms of basal ganglia thalamocortical interaction (Frank et al., 2007; Doya, 2008; Wiecki and Frank, 2013), related expansions in the study of decision-making and neuroeconomics (Glimcher, 2009) and increased appreciation of the behavioural and neuropsychiatric manifestations of primarily "subcortical" diseases (Ring and Serra-Mestres, 2002), there remain a lack of useful measures for the assessment and monitoring of motivational deficits. Subcortical pathology does not neatly impair discrete cognitive domains measured by commonly used cognitive tests (of e.g. language, memory or attention) that are helpful to identify focal *cortical* pathology (Burrell et al., 2014). Instead, basal ganglia disease causes non-specific impairments in many or all of these processes (Damasio, 1983; Cummings JL and Benson D, 1984; Crosson, 1992; Brown et al., 1997; Booth et al., 2007; Kotz et al., 2009; Obeso et al., 2014). The interconnectedness of subcortical structures makes them likely to cause dysfunction in multiple "cortical domains". For example, the basal ganglia have particularly strong connections with the frontal lobes. Consequent importance in executive function (Brown et al., 1997; Elliott, 2003) is demonstrable in the effects of basal ganglia dysfunction upon cognitive tests sensitive to frontal lobe damage (Cummings, 1993).

Such behavioural complexity is better understood when subcortical nuclei are considered as part of dynamic "circuits", with wide ranging influence on cognitive processes (Houk et al., 1995). Cortical - basal ganglia-thalamocortical (CBGTC) circuits have been anatomically and behaviourally described to include motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate "loops" (Figure 1.1 (Alexander et al., 1986; Middleton and Strick, 2000)). The dorsolateral prefrontal loop is important for the organisation of information to facilitate a response, the anterior cingulate circuit is required for motivated behaviour and the orbitofrontal circuit allows integration of limbic and emotional information into behavioural responses (Bonelli and Cummings, 2007). All of these processes are highly relevant to response selection. We might therefore call these three limbic loops "decision-making loops" (Figure 1.1). How might we interrogate the cognitive effects of damage to components of these loops?

The basal ganglia have a prominent role in influencing action selection through modulating the effects of reward learning (Kawagoe et al., 1998). The behavioural salience of this learning is reflected in rewarded decision-making (Bogacz and Gurney, 2007). Rewarded decision-making tasks might therefore capture the subcortical effects upon motivation. Established tasks include relatively complex measures of risk sensitivity and decision-making, such as the Iowa Gambling Task (IGT (Bechara et al., 1994, 1998, 2005)) and Cambridge Gambling Task (CGT (Rogers et al., 1999)) and simpler measures of willingness to take risk such as the Balloon Analog Risk Taking Task (BART) (Lejuez et al., 2002) in addition to a wide variety of probabilistic decision making tasks e.g. (Cools et al., 2001; Frank et al., 2004; Pessiglione et al., 2006) Delay discounting, wherein subjects are forced to choose between a smaller but sooner versus a larger but later reward, is also often used as a substrate of impulsive decision making (Petry, 2001; Alessi and Petry, 2003; Wittmann et al., 2007; Housden et al., 2010). These tasks, though perhaps more representative of "real world" decisions, are naturally more vulnerable to misinference, as a result of their complexity. Inferences drawn from experiments using gambling tasks such as the IGT have been criticised (Dunn et al., 2006; Lin et al., 2007; Chiu and Lin, 2007; Chiu et al., 2008; Lin et al., 2012) and basic predictions and assumptions called into question (Horstmann et al., 2012). These tasks are also not generally administered under time pressure (urgency) and may therefore index different traits and characteristics to speeded tasks such as those described in this thesis. Tasks without time pressure may be more cognitively demanding but, by allowing time for self-reflection, fail to capture "in the moment" impulsivity and become vulnerable to gambler's fallacies and other cognitive biases (Aragues et al., 2011).

In Parkinson's disease, batteries of tasks sensitive to frontal lobe function and probabilistic decision making tasks have been extensively employed (Robbins et al., 1994a; Cools et al., 2001, 2003) but seldom under significant time pressure. *Disease-specific* questionnaires have also been developed e.g. (Weintraub et al., 2009) but are yet to be generally validated, remain subject to observer bias and only capture historic traits. Neither current behavioural tasks nor questionnaires capture "in the moment" task motivation. The reliance of questionnaires upon subjective assessment of past behaviours makes negative responses unhelpful in predicting *future* behaviours. Behavioural tasks may be more useful in this regard, and there is evidence that improvement in task performance may mirror relevant clinical changes (e.g. Castrioto et al., 2014). Reaction time tasks are used extensively to study both healthy volunteers and patients. Saccadic tasks are amenable to use in animal studies that allow direct recording from relevant neural substrates and identification of the roles of specific neurotransmitters. This thesis considers the use of rewarded oculomotor decision making tasks under time pressure in humans as a means of interrogating motivated behaviours in the health and disease.

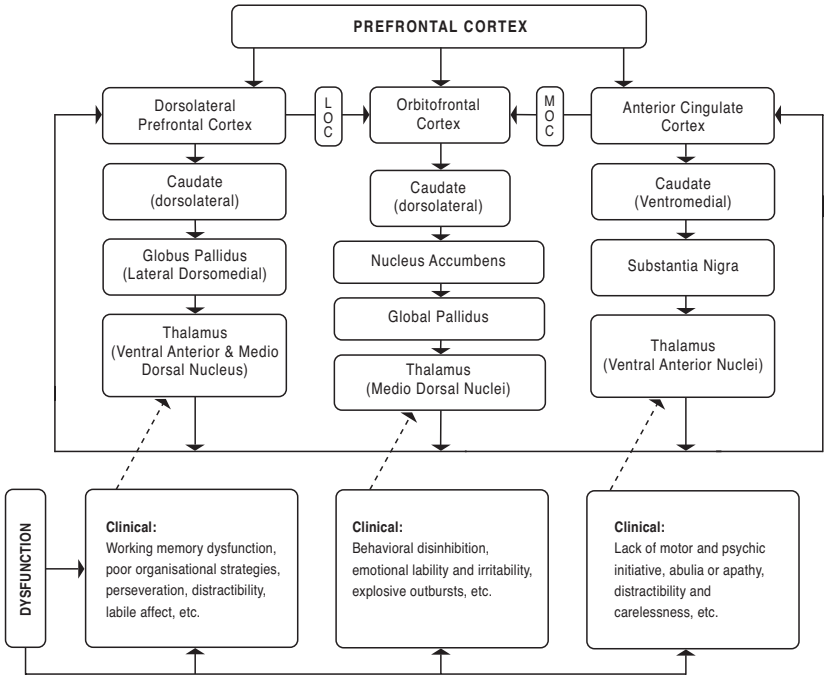



**Figure 1.1 Simplified view of pathways connecting prefrontal to subcortical structures involved in different aspects of executive control.**

There are five brain circuits originating in the frontal lobes and linking them as functional units to subcortical structures. Two of these have primarily motor functions and are not shown here. The other three (decision making) anatomical structures originate in prefrontal cortex, project to the caudate, connect to the globus pallidus and substantia nigra, and from there connect to the thalamus. A final link back to the frontal cortex does exist, and each circuit forms a closed loop. The dorsolateral cortex receives the majority of its distant afferent inputs by means of the superior longitudinal and uncinate fasciculi, and short-range association fibers (U-fibres) mediate local prefrontal connections. Medially, the orbitofrontal cortex connects to limbic structures by means of the uncinate fasciculus and to the ventromedial cortex through U-fibers. The orbitofrontal and ventromedial cortices are reciprocally interconnected, and it is likely that both are connected with the anterior cingulate by means of fibers of the rostral cingulum. LOC, lateral orbitofrontal cortex; MOC, medial orbitofrontal cortex. *Adapted from (Vale, 2008)*

### 1.1.2. Oculomotor performance as measure of loop function

Components and connections are shared between dynamic CBGTC loops. Despite anatomically distinct circuitry, damage to shared *components* of one circuit is likely to have effects within another. Developments in computational neuroscience have enabled the incorporation of multiple sources of evidence into models of these dynamic loops - from single cell recordings in animals to lesion and functional neuroimaging studies in humans (e.g. Wiecki and Frank, 2013). Yet, despite this great advance, we lack simple, rapidly administered and reproducible measures (or "biomarkers") of disrupted loop function. Do commonalities between the oculomotor loop and decision-making loops allow the assessment of problems with motivated behaviour from oculomotor responses? A proven way to interrogate these loops is through "saccadic decisions" (Glimcher, 2003; Frank and Claus, 2006; Kable and Glimcher, 2009). This thesis explores the possibility that eye movements allow specific insights into disruptions in motivation and behaviour leading to apathy and impulsivity following impairment to CBGTC loop function.

### 1.1.3. Dopamine modulates loop function for reward learning

Both disease processes and medication can disrupt loop function (Middleton and Strick, 2000). Healthy humans are uniquely advanced in their ability to flexibly modify choices according to feedback and thereby select the best adaptive response in particular behavioural, spatial and temporal contexts (Frank and Claus, 2006). Dopamine (DA) is important in modulating the cortico-basal ganglia circuitry to allow this flexible behaviour (Schultz, 1998; Daw, 2007; Robbins and Everitt, 2007). Thus the basal ganglia and DA are important in both action selection and reinforcement learning (Frank, 2005; Bogacz and Gurney, 2007; Humphries et al., 2012). Furthering our knowledge of the effects of disease and drugs upon disrupted basal ganglia thalamocortical loops, will increase our ability to both anticipate, prevent, recognise and treat cognitive and behavioural *dysfunction* in neuropsychiatric disease (Aarts et al., 2011; Cools et al., 2002; Dagher and Robbins, 2009; MacDonald et al., 2011).

### 1.1.4. Parkinson's Disease as a model of disrupted loop function and aberrant motivated behaviour

Parkinson's disease (PD) is an important example of a neuropsychiatric disease with high incidence and prevalence in the general population (Van Den Eeden et al., 2003). Disrupted front-striatal executive function in PD (Robbins and Cools, 2014) may explain the propensity for some patients with Parkinson's Disease to develop disorders of motivated decision-making, including apathy and impulsivity (Ahearn et al., 2012; Leroi et al., 2012; Sinha et al., 2013a; Aarsland et al., 2014). Studying cognition in patient populations is difficult due to the confounding effects of age, medical comorbidities and medications. This thesis attempts to address this problem by first describing experiments that investigate the effects of age, focal lesions of the basal ganglia and dopaminergic modulation, before consideration of patients with Parkinson's disease with and without recognised severe effects on their motivated behaviour. For comparison, I also study pathological gamblers without neurological disease.

### 1.1.5. Dopaminergic drugs may influence patients' decisions

Dopaminergic effects are especially relevant when considering the influence of medications on patients' behaviour (Czernecki et al., 2002; Pessiglione et al., 2006; Brooks and Piccini, 2006; Housden et al., 2010). Patients with PD have reduced dopaminergic transmission in the basal ganglia and subsequently suffer from impaired ability to learn about correct choices from trial and error (Cools, 2006). Optimal dopaminergic treatment of the motor disorder does not always correlate with ideal cognitive or behavioural outcomes (Weintraub, 2009). In some PD patients, particularly those treated with dopamine agonists, impulse control disorders develop, including pathological gambling (Avanzi et al., 2006; Driver-Dunckley et al., 2003; Gallagher et al., 2007; Molina et al., 2000; Voon et al., 2011a; Weintraub et al., 2010). We lack simple, clinical "biomarkers" to predict, assess and monitor behavioural dysfunction in these patients (Litvan et al., 2012; Svenningsson et al., 2012; Mollenhauer et al., 2014).

### 1.1.6 Saccades can provide an index of motivational behaviour

Saccadic decisions have demonstrated utility in the assessment of decision-making and are consistent with established models of cortico-basal ganglia circuitry and function (Wiecki and Frank, 2013; Cavanagh et al., 2014). Furthermore, saccadic decisions have been demonstrated to be sensitive to the effects of urgency (Reddi and Carpenter, 2000). This thesis will explore the use of rewarded oculomotor tasks to investigate decision-making behaviours in patients with impulsivity and/or apathy and attempts to modulate healthy volunteers performance with dopaminergic drugs. In this introduction, I first review the use of saccades in cognition (Section 1.2), the neurobiology of impulsivity (Section 1.3) and apathy (Section 1.4) and current understanding of the influence of dopamine on these constructs (Section 1.5). Latterly, I review what is known of the influence of age (Section 1.6) and disease, including Parkinson's Disease (Section 1.7) and Pathological Gambling (Section 1.8) on rewarded decision-making.

## 1.2 Saccade latencies as a cognitive measure

Much insight into the neurophysiological basis of perceptual decision-making in *non-human* primates derives from research on decisions about where and when to move the eyes e.g. (Glimcher, 2003; Gold and Shadlen, 2007; Kable and Glimcher, 2009; Schall, 2001, 2004; Smith and Ratcliff, 2009). The neural circuitry of the saccadic system is well described (Wurtz and Goldberg, 1989; Wurtz, 1996; Sweeney et al., 2007; McDowell et al., 2008). This circuitry is influenced by both basal ganglia and neocortical input and therefore its output (saccades) may reflect changes in brain areas important in rewarded decisions (Pierrot-Deseilligny et al., 1995; Hikosaka et al., 2000a; Pierrot-Deseilligny et al., 2004). This allows mechanistic inference about the human brain (Glimcher, 2003; Gold and Shadlen, 2007; Hutton, 2008; Kable and Glimcher, 2009). The importance of *dopaminergic* signalling in rewarded saccadic decisions is demonstrated by a number of landmark experiments in macaques (Ljungberg et al., 1992; Schultz, 1998, 2000; Schultz et al., 1997, 2000). Work by Hikosaka *et al.* on the *anatomy* of oculomotor decision making has shown the importance of neural substrates in the basal ganglia (Hikosaka and Sakamoto, 1986; Hikosaka et al., 1989a, 1989b). Combining this neurochemical and anatomical evidence has led to a more informed understanding of the neurobiology of saccadic decision making (Glimcher, 2001, 2003).

Eye movements have relatively few degrees of freedom, allowing fairly direct links between neurophysiology and behaviour to be established (Fuchs et al., 1985; Scudder et al., 2002). Saccades are ballistic, with stereotyped action depending on the direction, starting point, and distance the eyes need to move (Liversedge et al., 2011). The saccadic system is also a robust system which continues to function in spite of disease and drugs, making study of patients with motor disorders possible (Jones and DeJong, 1971; Lueck et al., 1990; Vidailhet et al., 1994; Mosimann et al., 2005; Rivaud-Pechoux et al., 2007). Saccades have previously been used to study cognitive processes in both health (e.g. Hutton, 2008; Kennard et al., 2005; Liversedge and Findlay, 2000) and disease (e.g. Braun et al., 1992; Mostofsky et al., 2001; Bagary et al., 2004; Michell et al., 2006; Golding et al., 2006; Hodgson et al., 2007; Antoniades and Barker, 2008; Blekher et al., 2009; Huddy et al., 2011; Jung et al., 2014). They have also been used to investigate the effects of drugs on both experimental volunteer subjects, patients and chronic substance abusers (Morgan et al., 2009). Furthermore, saccadic latency response distributions are well described in a variety of tasks e.g. (Carpenter and Williams, 1995; Carpenter, 2001; Reddi et al., 2003; Oswal et al., 2007; Story and Carpenter, 2009; Carpenter et al., 2009).

### 1.2.1 Cortical and subcortical areas interact to drive and control saccade production

The saccadic system is a useful candidate for study because common neural substrates are involved in both visual perception, motor production, and cognitive control (Schall, 1995a, 2001) (Figure 1.2). Cortical regions providing the "drive" for saccades include FEF, lateral intraparietal area (LIP) and supplementary eye field (SEF) (Wurtz and Goldberg, 1989). This drive encodes basic physiologic parameters including saccade direction and reaction time: In a "gap" paradigm, Functional magnetic resonance imaging (fMRI) blood-oxygen level dependent (BOLD) activation in the human FEF correlates with saccadic reaction time (SRT): Activity predicted both the type of eye movement (whether pro- or anti-saccade) and when the saccade would occur (Connolly et al., 2005).

### 1.2.2 The neural basis of oculomotor decisions

What about higher, "decision-making" processes requiring a saccadic response? By comparing prosaccades, antisaccades and Nogo trials, Brown *et al.* found that cortical areas (FEF, SEF, anterior cingulate cortex (ACC), intraparietal sulcus, and precuneus) exhibited similar activation patterns for prosaccadic and Nogo responses, suggesting that BOLD signal in these regions might reflect visual detection and attention processes rather than those required for saccade generation or inhibition. By contrast, right superior frontal sulcus, right supramarginal gyrus, and posterior cingulate sulcus activations were greater for Nogo versus pro-saccadic responses, suggesting that these areas are more important in saccade inhibition (Brown et al., 2006).

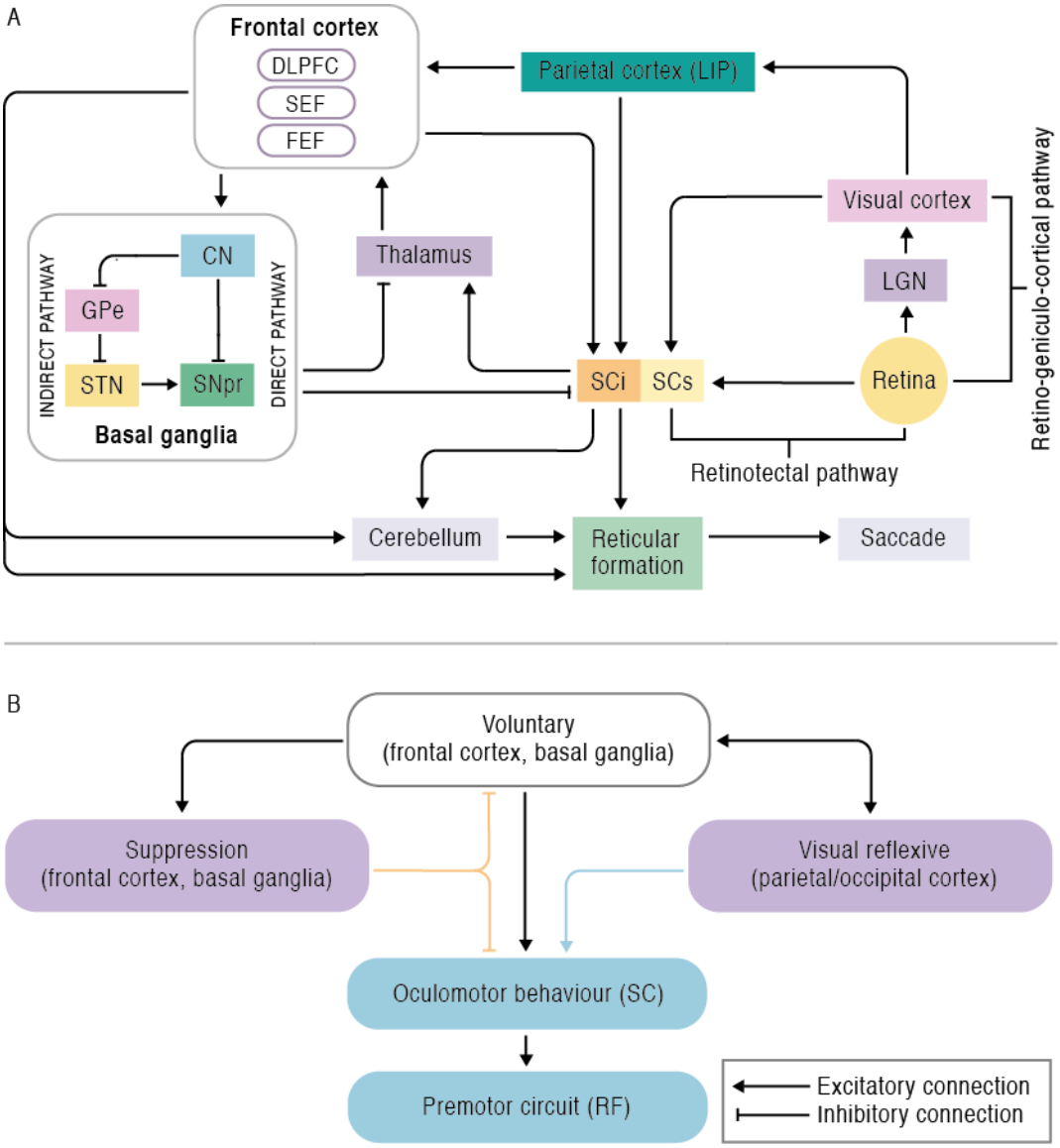



**Figure 1.2 Neural circuitry controlling saccadic eye movements.**

Schematics demonstrate:

**A** The anatomical substrates of oculomotor control, including inhibitory and excitatory connections between cortical and subcortical structures.

**B** An overview of cortical and subcortical structural roles

| | | | |
|---|---|---|---|
| *CN* | *Caudate Nucleus* | *LIP* | *Lateral Intraparietal Cortex* |
| *DLPFC* | *Dorsolateral Prefrontal Cortex* | *RF* | *Reticular Formation* |
| *FEF* | *Frontal Eye Fields* | *SC* | *Superior Colliculus* |
| *GPe* | *Globus Pallidus externa LGN Lateral Geniculate Nucleus* | *SEF* | *Supplementary Eye Fields* |
| | | *SNpr* | *Substantia Nigra pars reticulata* |
| | | *STN* | *Subthalamic Nucleus* |

*Adapted from (Munoz and Everling, 2004)*

fMRI in macaques performing an ocular "baseball task" [a Go/Nogo task in which subjects decide whether make to ocular pursuit of a moving spot target after deciding whether the target will cross a distal line segment] demonstrated task-related activity in the SEF, the FEF, the superior parietal lobule (SPL), and the right ventrolateral prefrontal cortex (VLPFC). The SPL and right VLPFC showed heightened activity only during ocular baseball, despite identical stimuli and oculomotor demands in the control task, implicating these areas in the *decision process*. Furthermore, the right VLPFC (but not the SPL) showed the greatest activation during Nogo decision trials. This suggests both a functional dissociation between these areas and a role for the right VLPFC in rule-guided inhibition of behaviour. In the SEF and FEF, activity was similar for ocular baseball and the control task. This suggests that SEF & FEF are tightly linked to motor commands whereas the SPL and VLPFC are implicated as cortical substrates of the decision process (Heinen et al., 2006).

Such discrete roles are almost certainly an oversimplification and reflect task specificity. For example, the SEF also has a demonstrable direct role in *rewarded* saccadic behaviour: In recordings from monkeys performing an oculomotor gambling task, SEF neurons were found to encode both the reward prediction error and the components necessary for its computation (i.e. expected and actual outcome). This suggests that the SEF has a role in the evaluation of value based decisions in the oculomotor domain (So and Stuphorn, 2012). Furthermore, a patient with a focal lesion of the SEF demonstrated specific deficits in *switching* from pro-saccadic to anti-saccadic responses (Parton et al., 2007): In an arbitrary stimulus-response associative learning task, the patient demonstrated a similar impairment in selecting the appropriate saccade from conflicting response choices, suggesting that SEF has a role in implementing control under conflict (Husain et al., 2003).

This plurality and task dependence of cortical effects is consistent with cortical regions not acting in isolation, but as part of dynamic circuits. There are well-recognised anatomical links with subcortical structures, which together form functional loops (Figure 1.1 (Alexander et al., 1986)). At the heart of these loops, the basal ganglia are involved in action selection, primarily by exerting powerful tonic inhibition that can be selectively reduced (Redgrave et al., 1999; Kropotov and Etlinger, 1999; Houk et al., 2007; Redgrave et al., 2011). The basal ganglia have two output pathways implicated in the movement control: the thalamocortical parallel pathways (Alexander et al., 1986) and the brainstem motor networks (Fawcett et al., 2005). The *oculomotor* circuit of the thalamocortical pathways projects back to the FEF and the SEF, thereby allowing reciprocal modulation. The action of these brainstem networks on saccadic eye movement has been demonstrated both anatomically, physiologically and pharmacologically (Hikosaka et al., 2000a). The superior colliculus acts as a final pathway for controlling saccadic eye movements, receiving projections from both the basal ganglia–superior colliculus pathway and the corticotectal pathways (Figure 1.2).

Saccades therefore reflect the output of the basal ganglia and may be a good indicator of their function (Yugeta et al., 2010). Both animal and human studies suggest that the basal ganglia are important in both the initiation and suppression of saccades in complex behavioural contexts, particularly by modulating the effects of reward (Tanaka et al., 2004). Both eye tracking and

pupillometry have shown that latent decision making processes can be interrogated through both eye movements and pupil size. For example, eye gaze dwell time and pupillometry correlated with drift rates toward targets and decision thresholds (Cavanagh et al., 2014). Through thoughtful experimental and task design, we hoped to establish oculomotor measures of rewarded decision-making sensitive to impairments including impulsivity and apathy. This requires consideration of known task designs and the expected corresponding responses.

### 1.2.3 Choice of Saccadic Task Design

The experiments in this thesis use both established and novel saccadic tasks. Straightforward eye movement tasks commonly used in cognitive experiments (Figure 1.3) generate reactive saccades with a unimodal distribution of saccadic latencies or reaction times (SRT) (Carpenter and Williams, 1995). In these tasks, saccades are driven by a stimulus ("Go" signal) at fixation or are provoked by the appearance of the target itself. Electrophysiology suggests that the latency of a saccadic response should be of the order of 70ms (Schall, 1995b). However, saccadic latencies in humans are much longer, at around 200ms. This 'oculomotor procrastination' (Carpenter, 1981) is explained by the interaction (braking) of the basic saccadic circuitry by higher order "decision makers". This interaction and its variability allow interrogation of saccadic latency for the purposes of cognitive research: Assuming that the basic saccadic circuitry has a fixed minimum latency, we infer that further delays (saccades at longer latency) are due to these higher order interactions (e.g. (Duka and Lupp, 1997; Hardin et al., 2007; Jazbec et al., 2006). Among other variables, the pattern of saccadic latencies is determined by the predictability of both the timing and spatial position of the cue (Engelken et al., 1991). Increasing the complexity of the task and/or modulating reward also modulate the pattern of saccadic responses (Sheliga et al., 2002; Stritzke et al., 2009).

### 1.2.4 Anticipatory Saccadic Responses

In some tasks, an earlier distribution of saccades is generated at shorter latencies than the standard reflexive saccades (Findlay, 1981; Bronstein and Kennard, 1987). This early distribution of saccadic responses (or "express saccades") is observed in "gap" tasks wherein the fixation target briefly disappears in advance of a saccade to the new target position (Fischer and Boch, 1983; Fischer and Ramsperger, 1984). Analysis of this effect shows that the majority of these earlier, express saccades occurred for trials where the target of the current trial was on the opposite side to the previous one (Carpenter, 2001). This suggests that in order to exploit anticipatory eye movements, saccadic task designs should employ alternating target directions. The more predictable the target location, the greater the number of express responses produced (Dickov and Morrison, 2006). These short latency responses enable probing of individual ability to anticipate targets/cues. Importantly, it does not appear that prior temporal (as opposed to spatial) knowledge of target onset in unrewarded tasks generates more express saccades (though such knowledge does reduce *reactive* saccade latencies (Gagnon et al., 2002)). By using a task that *rewards* short latency responses to predictable targets, alternating left and right (The Traffic Light Task, Chapter 2), we encouraged individuals to take risks in order to exploit their own anticipatory skill for increased task reward.

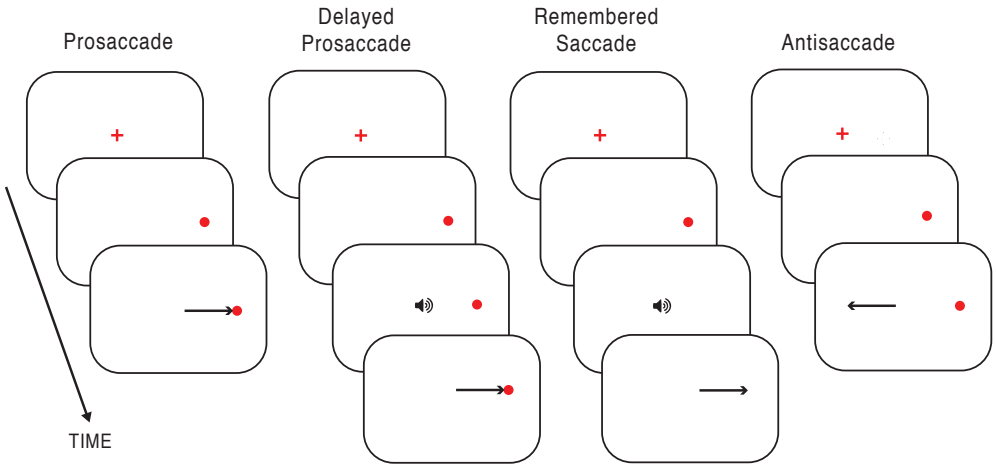



**Figure 1.3 Saccadic Tasks Commonly Used in Cognitive Research**

The four standard classes of saccadic task used in cognitive research. The arrow indicates the direction in which the eyes move in order to make a correct response.

Indicates an auditory "Go!" signal.

1) Prosaccade - the fixation target is extinguished simultaneously with the onset of a new, peripheral target to which a saccade is immediately made.

2) Delayed Prosaccade - the fixation target is extinguished simultaneously with the onset of a new, peripheral target to which a saccade is made immediately following a delay, the end of which is signalled by an auditory tone.

3) Remembered Saccade - the fixation target is extinguished simultaneously with the onset of a new, peripheral target that then disappears. On the presentation of an auditory "Go!" signal, the saccade is made to the remembered location

4) Antisaccade - the fixation target is extinguished simultaneously with the onset of a new, peripheral target. Saccades are made in the opposite direction to a target equidistant from the point of initial fixation.

*Adapted from (Hutton, 2008)*

### 1.2.5 Accumulator models describe multiple task-driven oculomotor latency distributions

The saccadic reaction time (SRT) to a new onset stimulus is short (200-250ms) and varies within a 'recinormal' distribution. That is to say that when histograms of SRT are plotted upon orthodox time and probability density axes, the distribution resembles a positively skewed Gaussian curve. This "skew" can be removed by plotting time (latency, SRT) using a reciprocal axis, rendering a normal shaped distribution. A simple statistical model which neatly replicates simple saccadic latency distributions (and possibly the underlying "neural representation" of likelihood) is described by LATER (Linear Approach to Threshold with Ergodic Rate) (Carpenter and Williams, 1995) (Figures 1.4A & B). In LATER, Log likelihood is used to predict saccade distributions on a reciprocal timescale, rendering the distribution linear on a "reciprobit" plot. The linear variables ($\mu$, $\sigma$) for mean latency and variance can then be used for comparison between individuals and groups.

Carpenter has suggested that the bimodal distribution of saccadic latencies in more complex eye movement tasks (such as gap, step and appearance tasks) might also be represented by a combination of two LATER "units" (Story and Carpenter, 2009). Furthermore, this type of accumulator modelling has been successfully applied to explain the competing directional demands in both countermanding and antisaccade tasks (Munoz and Everling, 2004; Noorani and Carpenter, 2014). Two opposing processes form the basis of a "race model" as also proposed by other authors (Band et al., 2003; Boucher et al., 2007). Most significantly for the novel designs used in experiments described in this thesis, the effects of a "maverick" LATER unit might explain the occurrence of short latency anticipatory responses (Roos et al., 2008) (Figure 1.4C). Could the presence and activity of such a "maverick" oculomotor decision-making process index impulsivity in rewarded behaviour? Impulsive subjects might have a maverick unit that fires earlier or reaches threshold more quickly. Apathy might mean a late firing or high threshold unit, or none at all. We used a combination of LATER units to model the responses to our novel, rewarded oculomotor task (Chapter 2).

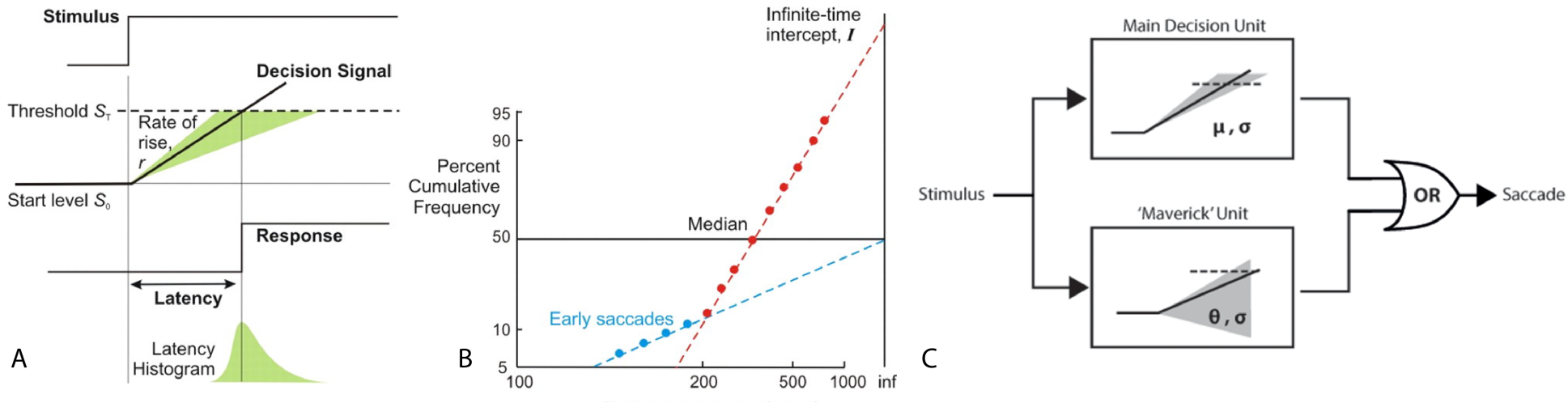



**Figure 1.4 The LATER model can explain simple saccadic tasks and complex tasks that generate multiple latency distributions.**

Carpenter's LATER (Linear Approach to Threshold with Ergodic Rate) model applies an accumulator model of decision making to saccade generation. At the time of target onset a decision signal starting from a baseline level ($S_0$) begins to rise at a constant rate (r) until it reaches a threshold ($S_1$) at which point a saccade towards the target is initiated. The rate of rise is assumed to vary randomly from trial to trial, with a mean and variance. Manipulations that result in changes in the baseline level of activity, the rate of rise or the threshold could all result in changes in saccade latency. Factors such as expectancies and the level of activation of the intention would presumably influence baseline levels of activation (Hutton, 2008). **A** On presentation of a stimulus, a decision signal starts to rise at a rate r from its initial value S0 until it reaches the threshold level $S_1$ for initiating action; on different trials, r varies randomly with a Gaussian distribution (μ, σ). As a result, a distribution of reciprocal latency over a number of trials is Gaussian. **B** Consequently, when a cumulative histogram is plotted using a probit axis and a reciprocal timescale (a reciprobit plot), they usually fall on a straight line, making an intercept I with the t = infinity axis. However, particularly under conditions of increased predictability, a small subsidiary population of aberrantly early saccades may sometimes be seen (blue), generating short-latency points lying on a different straight line, that typically has an intercept of zero. **C** A conventional LATER unit, with mean rate of rise μ and variance σ acts in parallel with a "maverick" unit having a greater variance but a rate of rise that on average is zero. Whichever unit reaches threshold first triggers the saccade.

*Adapted from (Oswal et al., 2007 and Roos et al., 2008)*

### 1.2.6 Using risk and reward to modulate anticipatory saccades

We hoped to generate a greater number of anticipatory responses in our task by disproportionately rewarding them. Others have previously demonstrated significant effects of reward upon saccadic preparation, by reducing the latency of reactive saccades in both animals (Hong and Hikosaka, 2008) (Figure 1.5) and humans (Milstein and Dorris, 2007). The role of subcortical brain areas in modulating such reward sensitivity has been demonstrated in animals. Studie s including direct recording of monkey brain neurophysiology have enabled investigation of the neural substrates of saccadic reward (McCoy et al., 2003; Hikosaka et al., 2006; Hong and Hikosaka, 2008; So and Stuphorn, 2010). Animal studies using memory guided saccades with an asymmetric reward schedule have demonstrated that visual and memory responses of caudate neurons are modulated by reward expectation (Kawagoe et al., 1998).

The relevance of dopaminergic projections from subcortical regions has been shown in an experiment which demonstrated projection of reward sensitive neurons from the internal segment of the pallidum (GPi) to the lateral habenula (Lh) (Hong and Hikosaka, 2008). Onward dopaminergic projections of Lh explain the role of this area in modulating cortico-striatal circuitry to allow reinforcement learning (Hong and Hikosaka, 2011). Pallidal projections to the lateral habenula and subsequent inhibition of dopaminergic neurons in the midbrain are also important in modulating saccadic reward learning (Hong and Hikosaka, 2008, 2013; Stephenson-Jones et al., 2013; Tachibana and Hikosaka, 2012). Other studies implicate dopaminergic, parietal, reward-sensitive cells (Schultz et al., 1997; Schultz, 2007). Hong and Hikosaka's task (Figure 1.5) was adapted as a measure of reward sensitivity for the experiments described in Chapters 3-7. Reward sensitivity has previously been demonstrated in human subjects with a reduction in latencies in both pro- and antisaccade tasks (Ross et al., 2011). Another study in humans found a negative correlation between expected value (reward probability × reward magnitude) and saccadic latency (Milstein and Dorris, 2007). Recent experiments suggest that *short* latency saccades are influenced by visual salience whereas longer latency saccades are affected by value (Schütz et al., 2012).

Two of our rewarded tasks examine risk aversion related to the timing of saccadic responses. The neural substrate of subjective *risk preferences* has only rarely been investigated using oculomotor tasks (McCoy and Platt, 2005a) and the risky element of the tasks used has not related to the timing of the eye movement nor has timing been related to the reward outcome e.g. (Ackermann and Landy, 2013; McCoy and Platt, 2005a; Stritzke and Trommershäuser, 2007; Stritzke et al., 2009).

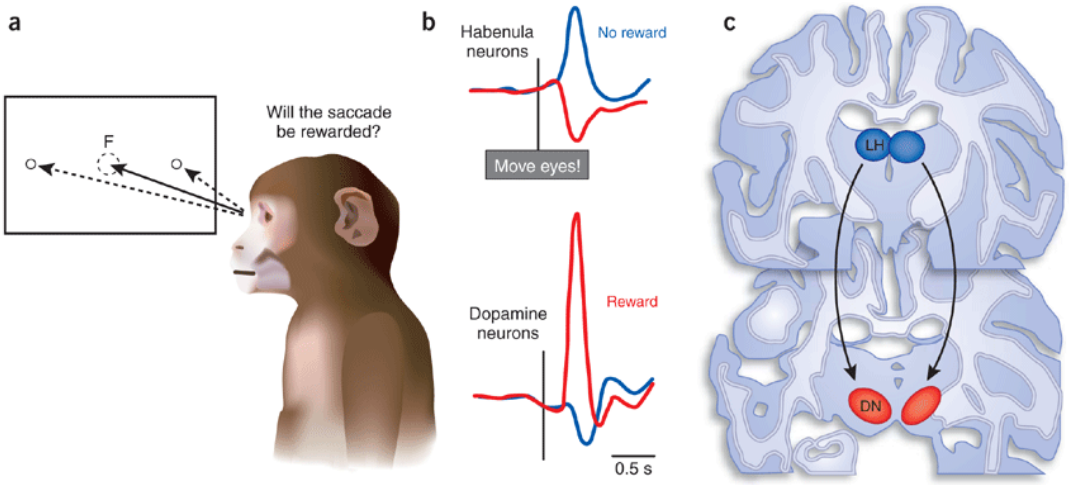



**Figure 1.5 The Lateral Reward Task**

Macaque monkeys fixated at the centre of screen (F). A visual target appeared either to the right or to the left of the fixation. They then made saccadic eye movements to the target. Saccades to one position were rewarded, but saccades to the other position were not. The relation between saccade position and reward was fixed for 24 consecutive trials and was then reversed in the next block of trials. (b) Habenula neurons showed a large increase of firing rate after saccade request for no reward and a decrease of firing after the request for rewarding saccade, whereas dopamine neurons were the opposite: increase of firing after request for rewarding saccade and decrease of saccade after request for unrewarding saccade. (c) Anatomical locations of primate lateral habenula (LH) and dopamine neurons (DN), and the flow of neural signals.

*(Hong and Hikosaka, 2008)*

Perhaps longer latency saccades (as produced by cognitively complex tasks) are more amenable to modulation by higher cognitive centres under the influence of reward? Support for this hypothesis comes from the differing effects of reward upon anti-saccades: In a study where the *target* indicated whether a saccade was to be rewarded or punished, both high rewards *and* punishments prolonged antisaccade latencies (Blaukopf and DiGirolamo, 2006) indicating that reward sensitivity and punishment avoidance can both increase cognitive "effort". However, in another study where the reward condition was known *in advance*, higher incentives reduced antisaccade *errors* without affecting latencies (Duka and Lupp, 1997). We designed rewarded oculomotor tasks sensitive to both saccadic latency and error rates in order to capture the effects of disease or drugs on either outcome measure. For example, impulsive oculomotor decisions might incorporate fast responses and anticipation but with excessive errors. In contrast, apathy might be manifest as few errors but little anticipatory behaviour and/or slow responses. The next two sections consider these constructs.

## 1.3 Impulsivity

Impulsivity is the tendency to act without adequate forethought (Broos et al., 2012). It is a complex personality trait that is characterized by an inclination to act hastily or inappropriately upon environmental stimuli or inner impulses without taking the consequences of these behaviours into account (Aichert et al., 2012). It is observed in the general population (Chamorro et al., 2012) but may be increased in patients suffering from a number of neurological and psychiatric disorders (Antonucci et al., 2006; Floden et al.; Djamshidian et al., 2012). These conditions include Parkinson's Disease (PD) (Ahearn et al., 2012; Leroi et al., 2011; Sinha et al., 2013b), Alzheimer's Disease (Lerner et al., 2007; Starkstein et al., 2006), frontal cortical lesions (Berlin et al., 2004; Floden et al., 2008) and fronto-temporal dementia (Chow et al., 2009; Eslinger et al., 2012). Impulsive decision-making is seen as part of the spectrum of healthy behaviour (so called "Functional Impulsivity" (Dickman, 1990)). Excessive ("Dysfunctional") impulsivity is a negative trait, however, leading to disruption and damage to the lives of patients and their families (Plutchik and Van Praag, 1995; Antonucci et al., 2006; Chamorro et al., 2012; Phu et al., 2014). Impulsive traits are a cause of significant morbidity (Phu et al., 2014; Smulders et al., 2014) and carer burden (Leroi et al., 2012).

### 1.3.1 Impulsivity is difficult to define and measure

Impulsivity is difficult to define (Dick et al., 2010; Evenden, 1999b), it comprises a cluster of lower order personality traits that include sensation seeking, risk taking, novelty seeking, boldness, adventuresomeness, boredom susceptibility, unreliability and unorderliness (Depue and Collins, 1999). No single personality trait underlies rash or impulsive action (Eysenck and Eysenck, 1977; Smith et al., 2007a; Whiteside and Lynam, 2001). This leads to poor correlations between measures (Evenden, 1999a; Meda et al., 2009). A lack of distinctive syntax and the tendency for the conflation of impulsivity with behavioural disinhibition (Goudriaan et al., 2008) generates further ambiguity and difficulty in making valid comparisons between reports. Furthermore, multiple modes of impulsivity are demonstrated to occur in the same individual or disease state, which makes independent assessment of each mode more troublesome (Huddy et al., 2013; Mackillop et al., 2014; Nombela et al., 2014).

It would therefore be useful to develop measures that might predict the need for (or measure a response to) treatment of this aspect of the conditions. For example, dopaminergic therapies are implicated in the development of impulse control disorders in patients with PD or restless leg syndrome (Voon et al., 2007; Voon and Fox, 2007; Cornelius et al., 2010; Voon et al., 2011b, 2011c; Leroi et al., 2013). Why do dopamine agonists cause impulsivity in some, but not all? Could a behavioural measure predict who might respond in this way?

### 1.3.2 Current Measures of Impulsivity

Current measures of impulsivity include self-report questionnaires and laboratory based, behavioural tasks. Despite being used interchangeably, the relationship between these measures is limited, suggesting that they may measure disparate aspects of impulsive behaviour (Keilp et al., 2005; Dalley et al., 2008; Cyders and Coskunpinar, 2011; Aichert et al., 2012; Cyders and Coskunpinar, 2012; Huddy et al., 2013). Self-reported indices of impulsivity include sensation seeking, risk-taking, lack of planning, perseverance, and acting on impulses (Whiteside and Lynam, 2001). Behavioural measures include inhibitory control tasks which assess the ability to suppress a prepotent response (response inhibition) or a conflicting, competing response (interference control), impulsive choice tasks (e.g. delay discounting) and time estimation measures (Dougherty et al., 2005; Friedman and Miyake, 2004; Nigg, 2000; Robbins et al., 2012). There is poor correlation between different behavioural measures and with self-report questionnaires (Aichert et al., 2012).

#### 1.3.2.1 Self-Report Questionnaires of Impulsivity

Impulsivity is a multidimensional construct, and different questionnaires have been developed to assess different aspects of the trait (Flory et al., 2006). Most focus on *dysfunctional* impulsivity, which is related to ineffective information processing and failure to inhibit inappropriate responses, whereas functional impulsivity is adaptive in being related to a rapid style of information processing (Dickman, 1990; Brunas-Wagstaff et al., 1994). One such measure, the Barratt Impulsiveness Scale (BIS-11, see Chapter 3 and Appendix (Patton et al., 1995; Stanford et al., 2009)) was chosen for the assessment of trait impulsivity in subjects of the experiments described here as it is widely used and validated (Congdon and Canli, 2005; Stanford et al., 2009). The questionnaire measures impulsiveness through items such as "I act on impulse" and "I consider myself always careful". Participants indicate how frequently each statement applies to them on a 4-point Likert scale (*never*, *occasionally*, *often*, and *almost always*). The scale has been applied in combined behavioural and neuroimaging studies e.g. (Horn et al., 2003) enabling inference about relevant brain areas. Furthermore, associations with oculomotor behaviour have been demonstrated (Roberts et al., 2011; Aichert et al., 2012) and sum scores have correlated with behavioural measures of impulsivity such as Go/Nogo commission errors and antisaccade error rates (Aichert et al., 2012).

Cloninger defines impulsive behaviour as the coexistence of four heritable temperamental traits: high novelty seeking (NS), low harm avoidance (HA), low persistence and high reward dependence (RD) (Cloninger, 1986). The Tri-dimensional Personality Questionnaire (TPQ, C R Cloninger 1987, see Appendix) contains 100 true/false items assessing three of these higher order dimensions of personality (NS, HA and RD). It is suggested that variation in each

dimension correlates with activity in a specific mono-aminergic pathway: Novelty seeking correlates with low basal dopaminergic activity, harm avoidance is due to high serotonergic activity and reward dependence is due to low basal noradrenergic activity (Cloninger, 1986). These links to monoaminergic neurotransmission led to the selection of this questionnaire for use in the chapters on dopaminergic modulation (Chapters 5 & 6).

#### 1.3.2.2 Performance-based measures of Impulsivity

Although these self-report measures of impulsivity measure a broad range of cognitive and behavioral styles in different social contexts, they are liable to subjective bias and are only capable of measuring stable traits. In order to assess further components of impulsivity, a variety of experimental paradigms have been developed to assess the ability to inhibit impulsive or inappropriate responses. These paradigms assess cognitive, motor, and emotional disinhibition (Dillon and Pizzagalli, 2007), delay-discounting in reward choices (Hariri et al., 2006), decision-making processes (Bayard et al., 2011) or time estimation biases (Davidson and House, 1978; Lennings and Burns, 1998). Behavioural measures are multifaceted - different tasks index various aspects of inhibitory function (Nigg, 2000; Friedman and Miyake, 2004; Dillon and Pizzagalli, 2007). A proposed categorisation (Table 1.1) includes five task types that measure variability in cognitive processes that contribute to impulsive behaviour (Dougherty et al., 2002; Marsh et al., 2002; Friedman and Miyake, 2004; Dougherty et al., 2005):

1. Prepotent response Inhibition

This refers to the ability to inhibit an already initiated response or to suppress dominant, automatic or prepotent responses. Tasks include Go/Nogo, Stop Signal Tasks, Continuous Performance Tasks and Antisaccade tasks.

2. Resistance to distractor interference

Tasks in which subjects must avoid interference from irrelevant distractors, such as the Eriksen Flanker Task, Stroop Task and Shape Matching Task.

3. Resistance to proactive interference

These tasks involve resisting memory intrusions of information, which was previously task relevant but no longer is. These include the Brown-Peterson task and Cued Recall Task.

4. Delayed response tasks

Impulsive subjects are thought to be less able to delay responding in order to obtain a larger reward in tasks including the two choice impulsivity paradigm and single key impulsivity paradigm.

5. Time discrimination tasks

Tasks wherein impulsive subjects demonstrate distorted judgments of elapsed time, such as in the TIME paradigm and the temporal discrimination task.

| Type | Example Tasks | Description | References |
|---|---|---|---|
| **Prepotent response Inhibition** | Go/Nogo | Suppress the inclination to make a previously reinforced response | (Marczinski and Fillmore, 2003; Kertzman et al., 2008) |
| | Stop Signal Task | Various modalities, inhibit previously entrained response when indicated by stop signal. | (Dimoska and Johnstone, 2007; Lipszyc and Schachar, 2010; Roberts et al., 2011; Fauth-Bühler et al., 2012) |
| | Continuous Performance task | Respond as quickly as possible to target stimulus, refrain from responding to rarer non-target | (Klee and Garfinkel, 1983) |
| | Antisaccade task | Suppress a reflexive saccade toward a cue and instead make a saccade away from the cue direction. | (Lueck et al., 1990; Duka and Lupp, 1997; Butler et al., 1999; Brown et al., 2006; Hood et al., 2007; Ross et al., 2011) |
| **Resistance to distractor interference** | Eriksen Flanker task | Identify target letter presented by itself or flanked by incompatible letters or symbols. | (Eriksen and Eriksen, 1974) |
| | Word naming task (Stroop) | Name target word, presented in green, alone or with distracter red word | (Stroop, 1935; Kane et al., 1994; Kertzman et al., 2006) |
| | Shape matching task | Same as above, but with shapes instead of words | (DeSchepper and Treisman, 1996) |
| **Resistance to proactive interference** | Brown–Peterson task | Learn and later recall successive lists made up of words taken from same category | (Kane and Engle, 2000) |
| | Cued recall task | View one of two lists of words, then recall word on most recent list, ignoring previous list words | (Tolan and Tehan, 1999) |
| **Delayed response tasks** | Two choice impulsivity paradigm | Choices between smaller reward more quickly, and larger reward with delay | (Dougherty et al., 2005) |
| | Single key impulsivity Paradigm | Respond as desired, size of reward related to length of delay between responses | (Dougherty et al., 2005) |
| **Distortions in elapsed time** | TIME paradigm | Estimate how much time has elapsed | (Dougherty et al., 2005) |
| | Temporal discrimination task | | (Bueti et al., 2008) |

**Table 1.1 Tasks used to measure various cognitive processes relevant to impulsive behaviour.**

#### 1.3.2.3 Current oculomotor measures of impulsivity

One way to measure impulsivity is by quantifying individual's inhibitory control (Bachorowski and Newman, 1985; Horn et al., 2003; Goudriaan et al., 2008; Roberts et al., 2011; Aichert et al., 2012). Prepotent response inhibition, defined as "the ability to deliberately suppress dominant, automatic, or prepotent responses", is a widely used measure of such inhibition (Friedman and Miyake, 2004). Prepotent response inhibition can be assessed with the antisaccade task (Hallett, 1978), the Stroop task (Stroop, 1935) (Stroop, 1935), the stop signal task (Logan et al., 1984) and the Go/Nogo task e.g. (Kertzman et al., 2008; Marczinski and Fillmore, 2003; Trommer et al., 1991). Prepotent response inhibition may also be dopaminergically modulated. In an $^{18}$F-fallypride fMRI study of the stop signal task (Ghahremani et al., 2012), striatal dopamine $D_2/D_3$ receptor availability was negatively correlated with speed of response inhibition (SSRT) and positively correlated with inhibition-related activation in frontostriatal neural circuitry. Correlations were strongest in the dorsal regions (caudate and putamen) of the striatum suggesting that $D_2$-like receptor function in humans plays a major role in the neural circuitry mediating behavioural control.

Oculomotor studies of impulsivity have used antisaccades and stop-signal reaction time in saccadic countermanding tasks e.g. (Boucher, 2007; Hanes and Carpenter, 1999). In antisaccade tasks (Figure 1.3), participants suppress a highly automated, reflex-like prosaccade to a sudden onset peripheral target and instead initiate a saccade of the equivalent magnitude in the opposite direction. Latencies (of pro- and anti- saccades) and numbers of pro-saccadic errors are performance indicators. Impulsive subjects make more errors and/or generate longer latency antisaccade responses (Hutton et al., 2004). This relationship is so reproducible among conditions associated with impulsive behaviour and fronto-striatal executive dysfunction, that poor antisaccade task performance has been used as evidence that other conditions (such as Tourette syndrome) are due to impairments of similar circuitry (Dursun et al., 2000; Jackson et al., 2011). However, task response is not easily predictable in such conditions: Patients with ventrolateral frontal cortical damage made more errors on an oculomotor rule switching task (Hodgson et al., 2007) whereas patients with Tourette's were *more* controlled in switching than healthy subjects, despite slowed prosaccadic latencies – suggesting that the task may detect adaptive behaviours (i.e. *increased* cognitive regulation (Jung et al., 2014)).

Stop-signal tasks cue a response using a visual or auditory stimulus. "Respond" trials are interleaved with "Stop" trials. In the latter, a stop-signal is presented shortly after the cue and is intended to prevent the cued response. Measurement of the latency with which the stop-signal remains effective provides another index of impulsivity. Iterative task designs are used to find the shortest stop signal interval that successfully inhibits the response. This stop signal reaction time (SSRT) is used as an index of subjects' ability to inhibit a previously initiated motor command. The longer the effective SSRT, the less impulsive that individual is thought to be. Animal recordings and human functional imaging studies suggest that stop-signal inhibition is implemented by interactions between frontal (cortical) and subcortical regions (Aron and Poldrack, 2006; Li et al., 2006; Schall and Boucher, 2007; Verbruggen and Logan, 2008). Countermanding saccade tasks employ a similar design, wherein most trials require a saccade

to a sudden onset peripheral target, but others display a stop-signal at variable delays following the target onset. Performance in both tasks has been simulated by a race model in which the process driving a response can be interrupted by a 'stop signal' if received before that process reaches a certain threshold (Hanes and Carpenter, 1999; Noorani and Carpenter, 2014).

In Go/Nogo paradigms, subjects respond with a fast motor response when a frequent "Go!" stimulus appears but withhold their response when an infrequent "Nogo" stimulus is presented. Responding to the go-stimulus is made prepotent by presenting more Go stimuli than Nogo stimuli. The key indicator of impulsivity is the frequency of commission errors — i.e. failure to suppress the response to the Nogo stimulus (Trommer et al., 1991; Rubia et al., 2001; Horn et al., 2003). Similar neural substrates to those implicated in stop-signal tasks have been demonstrated in a meta-analysis (Simmonds et al., 2008). Both manual and saccadic cued inhibition tasks of this type have been compared: Roberts *et al.* employed both behavioural inhibitory control tasks (Cued Go/Nogo task [manual], manual stopping task, visual stopping task [saccadic countermanding] and a delayed ocular response task [DORT]) and impulsivity measures (BIS, UPPS & Impulsiveness Questionnaire) to compare adults with ADHD with age matched controls. They found that eye movement tasks (but not manual ones) related to specific domains of self-reported impulsivity in the ADHD group (but not the control group) (Roberts et al., 2011).

Cirilli and others used an oculomotor pursuit task that evoked anticipatory saccades. They compared basic characteristics such as latency and velocity with UPPS scores, finding correlations between distinct UPPS factors and oculomotor anticipation parameters (Cirilli et al., 2011). Behavioural and self-report correlations are also reported between BIS-11 impulsivity and commission errors and directional errors on an antisaccade task (Aichert et al., 2012).

### 1.3.3 Summary

We aimed to design and adapt oculomotor tasks which indexed reward related impulsivity by attempting to modulate anticipatory saccades in particular. To our knowledge, no one else has previously explored this potential index of rewarded decision-making. The outcomes of these tasks are compared with the results of established (self report) measures of impulsivity - the BIS-11 and the TPQ in Chapter 3.

## 1.4 Apathy

Although many advances have been made in understanding how rewards – both extrinsic and intrinsic – influence behaviour (Berridge, 2004; Dreher and Tremblay, 2009; Schultz, 2000), one area that has been relatively neglected until recently is the study of apathy (Starkstein and Leentjens, 2008). Apathy is a reduction in self-generated, purposeful behaviour (Levy and Dubois, 2006). It is a common behavioral symptom of aging, in people with or without dementia (Ishii et al., 2009; Brodaty et al., 2010) and is widespread in mild forms in many people (Lampe et al., 2001). Apathetic persons lack the drive to explore and exploit their environment and, as a result, do not contribute or engage, either socially or in the work place. Such a state is sometimes considered to be simply one extreme of normality. It is clear, though, that apathy can be a severe, pathological behavioral state in degenerative brain disorders such as Alzheimer's and Parkinson's disease where it can be a major contributor to disease burden (Marin, 1991; Starkstein and Leentjens, 2008; Leroi et al., 2012).

### 1.4.1 Apathy, like impulsivity, is poorly defined and quantified

Apathy is caused by both primarily neocortical pathology (Starkstein et al., 2001; Levy and Dubois, 2006; Chow et al., 2009) and is seen in focal *lesions* of the basal ganglia (Mendez et al., 1989; Caplan et al., 1990; Bhatia and Marsden, 1994) as well as primarily subcortical neurodegenerative disorders including Parkinson's disease (Drapier et al., 2006; Czernecki et al., 2008; Leroi et al., 2011; Ahearn et al., 2012; Sinha et al., 2013a). It is associated with cognitive decline (Starkstein et al., 2006; Onyike et al., 2007) and it is also seen in depression (from which it is dissociable (Levy et al., 1998; Oguru et al., 2010; Butterfield et al., 2010; Kirsch-Darrow et al., 2011)) where it has been associated with frontal (executive) dysfunction. The syndrome is therefore attributable to diffuse and disparate changes in the brain. As such, it is difficult to develop a biological model. Nonetheless, apathy is emerging as a cognitive state that can be manipulated experimentally to understand the neurobiology of motivation (Schmidt et al., 2008). Apathy, like impulsivity, is not a unitary construct but is rather a multifaceted condition arising from dysfunction in several candidate decision-making mechanisms (Levy and Dubois, 2006). A number of rating scales exist for the measurement of apathy (Marin et al., 1991; Sockeel et al., 2006; Clarke et al., 2007; Leentjens et al., 2008; Pedersen et al., 2012; Radakovic and Abrahams, 2013), however, behavioural measures have rarely been employed. Here I propose the use of oculomotor, rewarded, decision-making tasks as additional valid measures of *low* motivational states.

### 1.4.2 The roles of the frontostriatal circuits and dopamine in apathy

Although many brain regions are activated by reward, a wide range of studies have now demonstrated that the basal ganglia, orbito-frontal cortex (OFC), and ventromedial prefrontal cortex (vmPFC) make a particularly important contribution to value-based decision-making (Haber and Knutson, 2010). Corticobasal ganglia circuitry is strongly implicated in the functional anatomy of apathy (Levy and Dubois, 2006) with dopamine playing a critical role in modulating behavioural sensitivity to reward (Schultz, 2007). Damage to the medial frontal cortex in humans leads to apathy: Patients demonstrate 'abulia': reduced initiation of behaviour, lack of interest in their surroundings and loss of spontaneous emotional expression

(Starkstein and Leentjens, 2008). Recent functional imaging in healthy humans implicates medial frontal and striatal regions in effort-based decision-making (Croxson et al., 2009). It is perhaps unsurprising, therefore, that a similar state to that in frontal patients occurs after focal lesions of the basal ganglia (Bhatia and Marsden, 1994; Laplane and Dubois, 2001; Schmidt et al., 2008). I report on such a case in Chapter 4.

In a previous report (Schmidt et al., 2008), 13 patients with apathy (or "auto activation deficit" (AAD)) secondary to bilateral striato-pallidal lesions were compared with 13 Parkinson's disease (PD) patients. Though the 2 groups did not differ in their externally instructed grip strength or skin conductance responses for monetary rewards, the AAD patients failed to differentiate between monetary incentives in their grip strength. The authors concluded that bilateral striato-pallidal lesions specifically disconnect motor outputs from the patients' evaluation of potential reward. In the absence of other human studies, we might look to the animal literature: Research in animal learning has suggested that a useful framework for understanding goal-directed actions might be in terms of how animals value action outcomes (Dickinson and Balleine, 1994). From this perspective, obtaining valued rewards is the ultimate driver of behavior. But what happens if the system for valuing outcomes no longer operates? One consequence might be lack of motivation to act, or apathy.

There is good evidence for such a theory: Lesions of the medial frontal lobe, involving the anterior cingulate cortex, affect how much effort rats are willing to invest for rewards (Rudebeck et al., 2006; Schweimer and Hauber, 2005; Walton et al., 2002, 2003). Rats are also rendered 'anergic' – employing less effortful feeding behaviour – by disruption of dopaminergic transmission in the nucleus accumbens (Font et al., 2008) or the GABAergic* system in the ventral pallidum (Farrar et al., 2008a). Apathy also correlates with the degree of atrophy of the nucleus accumbens in patients with PD (Carriere et al., 2014). Moreover, functional imaging in healthy humans implicates medial frontal and striatal regions in effort-based decision making (Croxson et al., 2009), consistent with the view that frontostriatal dysfunction might be a key component of apathy in human diseases (Cummings, 1993; Levy and Dubois, 2006), specifically by rendering patients unwilling to make efforts for rewards. Behavioural support for such a view comes from the finding of impaired Iowa Gambling task performance in brain injured patients with apathy (Njomboro et al., 2012) and, similarly in PD patients with apathy compared to those without (Martínez-Horta et al., 2014).

These results also point to the possibility that apathy might be susceptible to modulation by dopamine (see Section 1.5). However, no previous study has reported on the effects of dopaminergic medication on focal basal ganglia lesion patients with apathy. In Chapter 4, I discuss the results of attempts to improve the motivational state of a patient who suffered from apathy following bilateral ischaemic lesions of the GPi. Internal globus pallidus (GPi) neurons have been shown to demonstrate reward-related activity on oculomotor tasks (Hong and Hikosaka, 2008; Shin and Sommer, 2010) thus the use of oculomotor tasks to monitor impairment and improvement in this case is theoretically and empirically justified.

**GABA* – *γ-Amino Butyric Acid*

### 1.4.3 Apathy and oculomotor behaviour

To our knowledge, oculomotor tasks have not previously been used to study apathy in human subjects. However, in non-human primates, rewarded behaviour has frequently been studied using eye movements. Recordings from the globus pallidus have demonstrated reward-related activity when macaque monkeys perform eye movement tasks (Hong and Hikosaka, 2008; Shin and Sommer, 2010). Oculomotor paradigms have shed light upon both brain regions and neurotransmitters, such as dopamine, that play a key role in making choices and learning from their outcomes (Hikosaka, 2007; Hikosaka et al., 2000a; Schultz, 2007, 2002). It is therefore proposed that oculomotor tasks are suited to the study and potential modulation of apathy in humans. One means of modulating rewarded oculomotor behaviour is through dopaminergic medication.

## 1.5 Dopaminergic roles in rewarded decision-making

A wide range of studies has demonstrated that dopamine might play a central role in modulating sensitivity to reward (Wise, 2004; Schultz, 2007) with the basal ganglia, medial and orbitofrontal cortex (OFC), often implicated in value-based decision making, forming part of a 'reward circuit' (Haber and Knutson, 2010; Pessiglione et al., 2007). Dopaminergic neurotransmission is also integral to two major theories of impulsive personality: Gray's reinforcement Sensitivity Theory (Gray, 1970) and Cloninger's Psychobiological model of personality (Cloninger et al., 1993). Dopaminergic neurons encode reinforcement prediction errors (Schultz et al., 1997; Schultz, 1998; Maia, 2009) which are important in many reinforcement learning models. Dopaminergic neurotransmission is critical in many parts of the CBGTC loops (Alexander et al., 1986). It has been proposed that these loops integrate action selection by the basal ganglia with action plans generated in the cortex (Frank, 2005; Mink, 1996). Correlations are observed between impulsive personality traits and dopamine dependent changes in fronto-striatal activity during a working memory task (Cools et al., 2007). Latterly more specific roles have been established in effortful decision making, overcoming the cost of making efforts to obtain desired goals (Niv et al., 2007; Kurniawan et al., 2011). There is increasing evidence that dopaminergically innervated striato-nigro-striatal connections form the basis for functionally specific effects of appetitive motivation on cognition. This appetitive motivation can induce cognitive improvement or impairment depending upon task demands (Aarts et al., 2011).

### 1.5.1 Dopamine modulates both apathy and impulsivity

There is strong evidence that dopaminergic medications play a role in the provocation of impulse control disorders in patients with Parkinson's Disease and Restless Leg Syndrome ((Weintraub, 2009; Cornelius et al., 2010; Voon et al., 2011a; Grosset et al., 2011); see section 1.7). Evidence for dopaminergic modulation of apathy is weaker and relies upon limited reports of the efficacy of dopamine agonists and other agents which modulate dopamine levels (Roth et al., 2007; Ishizaki and Mimura, 2011). We might therefore try to infer further information from experiments in the animal literature.

### 1.5.2 Dopamine and reward: evidence from animal experiments

Both drug effects and lesion studies that target dopaminergic circuitry in animals inform the reward literature. Lesions of the medial frontal cortex affect how much effort rats are willing to invest for rewards (Rudebeck et al., 2006; Walton et al., 2002, 2003; Schweimer and Hauber, 2006). Rats are rendered 'anergic'- employing less effortful feeding behaviour by disruption of dopaminergic transmission in the nucleus accumbens (Farrar et al., 2008a). Receptor specific effects and differing effects in high and low baseline performers have also been demonstrated. A five choice serial reaction time task was employed to investigate the role of D1 and D2-like receptors in rat medial prefrontal cortex (mPFC). Sulpiride (a D2 receptor antagonist) had no effects on task performance, whereas a D1 antagonist and a D1 agonist had opposing effects on rats classed as pre-treatment 'high' and 'low' performers: The antagonist impaired the accuracy of attentional performance in baseline high performers (but did not in those animals who performed poorly at baseline) whereas the agonist enhanced accuracy in poor baseline performers (but did not in the high performers) (Granon et al., 2000). There is evidence, also from rat experiments, that this baseline performance is reflective of endogenous, baseline DA levels. That is to say that low DA levels accompany poor performance, which is improved by DA agonists. High levels of DA are associated with good performance, which is impaired by the same agonists (Phillips et al., 2004). Both excessive and insufficient DA levels in the PFC impair rat performance in delayed alternation tasks (a measure of spatial working memory) (Zahrt et al., 1997). There are, therefore, multiple pieces of evidence for an optimal dopamine "level" for various task demands. This lends itself to the so-called "inverted U-shape" relationship between subjects' performance modulated by drugs (Figure 1.6).

### 1.5.3 Bidirectional effects: evidence from human experiments

Studies in humans (both healthy volunteers and patients) also suggest that dopaminergic modulation can either *improve* or *impair* cognitive function, depending upon the task and endogenous DA levels in the cortico-striatal circuitry (Cools, 2006). In human subjects performing working memory tasks, high baseline performance was impaired by bromocriptine (a D2 agonist) whereas those subjects who performed poorly at baseline seemed to improve after drug administration (Kimberg et al., 1997). These effects were task specific. It is also possible that there was an interaction with training effects. The study did not train the subjects prior to the drug/placebo sessions and no analysis of order effects is presented. Moreover, the authors admit that their attempts to rule out regression to the mean were not completely successful. In the drug effect experiments reported in Chapters 5 and 6, we avoided training effects by using a 3-stage protocol, with a training session before subjects took either drug or placebo.

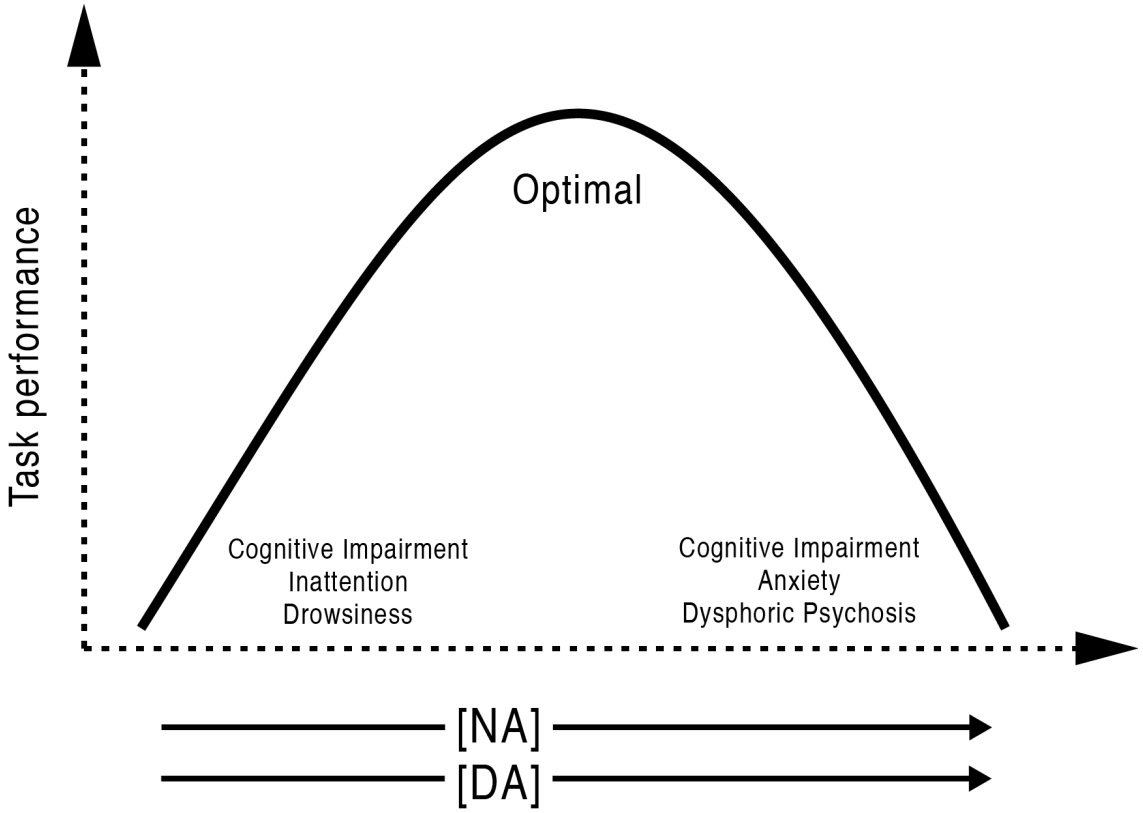



**Figure 1.6 The inverted U-shape relationship between neurotransmitter levels and performance.**

Noradrenaline (NA) and dopamine (DA) neurotransmission in the prefrontal cortex and executive function. NE and DA in arrows represent increasing levels of stimulation.

*Adapted from (Blier and Briley, 2011)*

In a study of spatial working memory, beneficial effects of methylphenidate (MPH, see section 1.5.6 and Chapter 6), which has dopaminergic effects, were greatest in those subjects who had lower baseline working memory capacity (Mehta et al., 2000). Similarly, MPH improved performance in working memory, visual search and attentional set shifting in children with ADHD. However, the working memory effect was most prominent in those with worst baseline performance (Mehta et al., 2004). Multiple pieces of experimental evidence therefore point to an "inverted-U-shape" function relating DA levels and performance (Arnsten, 1998). In other words, there may be an optimal DA level for specific cognitive functions: Too little endogenous DA leads to poor performance, which may be improved by medication. Conversely, having DA levels further increased might impair those with optimal DA levels at baseline for the same cognitive task.

### 1.5.4 Apathy in PD is modulated by Dopamine

There is some evidence that apathy improves following dopaminergic therapies. Young, drug-naïve PD patients were compared to another PD group, recently medicated with dopamine agonists, and healthy controls (Bodi et al., 2009). They performed a feedback-based probabilistic classification task. Unmedicated patients had selective deficits in reward processing and novelty seeking – personality traits associated with apathy (Pluck and Brown, 2002; Shulman, 2007). Introduction of dopamine agonists ameliorated these deficits but also diminished the correlation between punishment processing and harm avoidance in a feedback based probabilistic classification task. The authors concluded that this might explain the development of impulse control disorders in the PD population, particularly those treated with agonists. Can these drugs be used to overcome apathy in other conditions, such as patients with focal basal ganglia lesions?

Little consensus exists in the treatment of apathy. A review of the treatment of 7 patients with apathy from a variety of underlying causes included almost as many different agents (amantadine, amphetamine, bromocriptine, bupropion, methylphenidate, and selegiline) (Marin et al., 1995). The commonality between these agents is activity upon dopaminergic transmission – either by acting at the receptor or on preventing reuptake. It is widely suggested that alterations in dopaminergic neurotransmission are responsible for decision making impairments in Parkinson's disease (e.g. (Cools, 2008)). Furthermore, it is thought that the relative preservation of the ventral striatum (compared to the dorsal striatum, which is affected early in the disease) in concert with the therapeutic use of levodopa and/or dopaminergic agonists leads to the behavioural changes in discussion (Cools, 2006). This theory is supported by current knowledge of dopaminergic circuitry, behavioural and neuroimaging experiments in both patients and healthy volunteers (Funkiewiez et al., 2006) and is consistent with computational models which explain performance in some tasks (e.g. (Frank et al., 2007)). Performance is poor in those with low endogenous levels, and therefore increasing availability might *improve* the task outcome. However, supplementation of already optimal performers causes *deterioration* in performance.

In chapters 5 and 6, I investigate the effects of two drugs known to have dopaminergic effects – levodopa (L-dopa) and methylphenidate (MPH).

### 1.5.5 The cognitive effects of levodopa (L-dopa)

Levodopa is the *laevo* optical stereoisomer of the L-configurational form of dopa and is used for the symptomatic treatment of Parkinson's disease (Brogden et al., 1971). Though cognitive effects of dopaminergic modulation have been recognised experimentally (Cools et al., 2002; Dolan et al., 1995; Goldman-Rakic et al., 2004), cognitive effects have not been the main treatment aim of dopaminergic drugs in Parkinson's disease where levodopa is primarily used to treat motor symptoms of the disorder. Nevertheless, there are well-recognised cognitive and psychiatric effects (Choi et al., 2000; Molloy et al., 2006). Furthermore, levodopa has been implicated in development of impulse control disorders in Parkinson's patients (Weintraub et al., 2010; Grosset et al., 2011; Voon et al., 2011c). This suggests that levodopa can modulate decision-making. That suggestion is supported by experiments which demonstrate changes in risk evaluation in healthy volunteers (Pessiglione et al., 2006; Pleger et al., 2009) and reward-based decision making in patients (Graef et al., 2010).

#### 1.5.5.1 L-dopa effects upon reward learning

Human experiments using behavioural tasks and fMRI have begun to reveal the extent of L-dopa's wide-ranging effects. These include "bottom-up" effects upon low-level somatosensory decisions (Pleger et al., 2009). L-dopa enhanced the effects of higher anticipated reward, which then improved tactile decisions, in contrast to Haloperidol (a DA antagonist), which impaired task performance. These reward and DA effects correlated with changes in striatal and orbitofrontal BOLD signal, demonstrating a clear association between drug administration, task dependent learning and corticostriatal circuitry. L-dopa appears to enhance reward expectation e.g. (Sharot et al., 2009) and can restore reward prediction errors, which decline with age (Chowdhury et al., 2013). It also increases preference for earlier rewards, increasing temporal discounting, for example (Pine et al., 2010). This demonstrates evidence for dopamine enhancing temporal impulsiveness. Notably, L-dopa had no effect upon the *time taken to decide* in these studies. However, in a study in healthy volunteers which used *repeated dosing* of L-dopa for 5 days, it was found that L-dopa led to enhanced speed, overall success and long term retention of novel word learning, in a dose-dependent manner (Knecht et al., 2004). Novel word learning was faster in subjects who had received L-dopa than those who had received placebo. Remarkably, the L-dopa induced improvements in word learning were maintained 1 month after the study. L-dopa has also been associated with more frequent choice of a high-probability gain choice compared to haloperidol (Pessiglione et al., 2006). There was no effect on the frequency of choosing a low probability loss. This meant that L-dopa treated subjects won more money in the task overall. The drug induced behavioural differences were correlated with changes in BOLD response of opposing direction in the striatum, suggesting it as an anatomical substrate for the L-dopa induced heightened reward sensitivity.

### 1.5.5.2 L-dopa effects upon risk, time perception, reaction times and saccades

In addition to learning to associate optimal saccadic performance with reward, the oculomotor tasks in this thesis require subject assessment of risk, optimal time perception and saccadic performance. What is known of L-dopa effects upon these parameters?

In the only reported study of risk found, L-dopa had no effect on subject's risk evaluation. The authors propose that the main dopaminergic effect upon decision-making is therefore through modulation of the response to reward (Symmonds et al., 2013). There is evidence to suggest that the role of the basal ganglia in producing internal representations of time is dopaminergically mediated (Rammsayer, 1993) by regulation of an internal 'pacemaker' (Buhusi and Meck, 2002). L-dopa reduced variance in the responses and shortened latencies in a key press task (Rihet et al., 2002). L-dopa has also been found to affect time interval estimation - lengthening estimates in the 'seconds' range without changing reaction time (Rakitin et al., 2011). One study in healthy volunteers found fewer correct anti-saccades following L-dopa administration, but no effects on reflexive saccades (Duka and Lupp, 1997). The authors noted that this effect was directly opposed to the effect of incentive (monetary reward) on the task, which increased accuracy.

There is more extensive evidence of L-dopa effects in the patient literature. Electro-oculographic data demonstrated improved saccade *amplitudes* following a single dose of L-dopa given to PD patients but no significant changes in latency (Rascol et al., 1989). A more recent study has found that L-dopa slowed reactive saccades (pro-saccades) in a PD patient population (Michell et al., 2006) compared to baseline measurements 'off drug'. This effect was not uniformly present in all patients, and the group effect appears to have been driven by a few individual responses. Another group have replicated this finding, however, and also found that L-dopa (at the patient's usual doses) improved the accuracy (reduced the error rate) of voluntary anti-saccades (Hood et al., 2007).

### 1.5.5.3 L-dopa and cognition in Parkinson's Disease

In the PD patient population, there is a large degree of inter-individual variability in the response of cognitive symptoms to L-dopa. The cognitive effects of dopaminergic drugs in PD are both task specific and vary with motor "on"/"off" states (Leroi et al., 2013). L-dopa withdrawal studies have demonstrated that the drug improves cognition (on a conditional associative learning task) in some patients, but causes deterioration in others (Gotham et al., 1988). Consistent with the inverted U-shape hypothesis (Cools and D'Esposito, 2011), patients who performed particularly poorly off the drug gained the most benefit from L-dopa, whereas those who performed well off drug were impaired by its administration. This and similar findings have lead to the so-called "Dopamine overdose" hypothesis ((Kwak et al., 2010; Colzato et al., 2012; Cilia, 2012) Figure 1.7). This suggests that the doses of L-dopa required to replace endogenous neurotransmitter in damaged brain areas lead to an *overdose* of other (intact) brain areas (Gotham et al., 1988; Swainson et al., 2000; Cools et al., 2001; Frank et al., 2004; Frank, 2005; Cools et al., 2006; Cools, 2006).

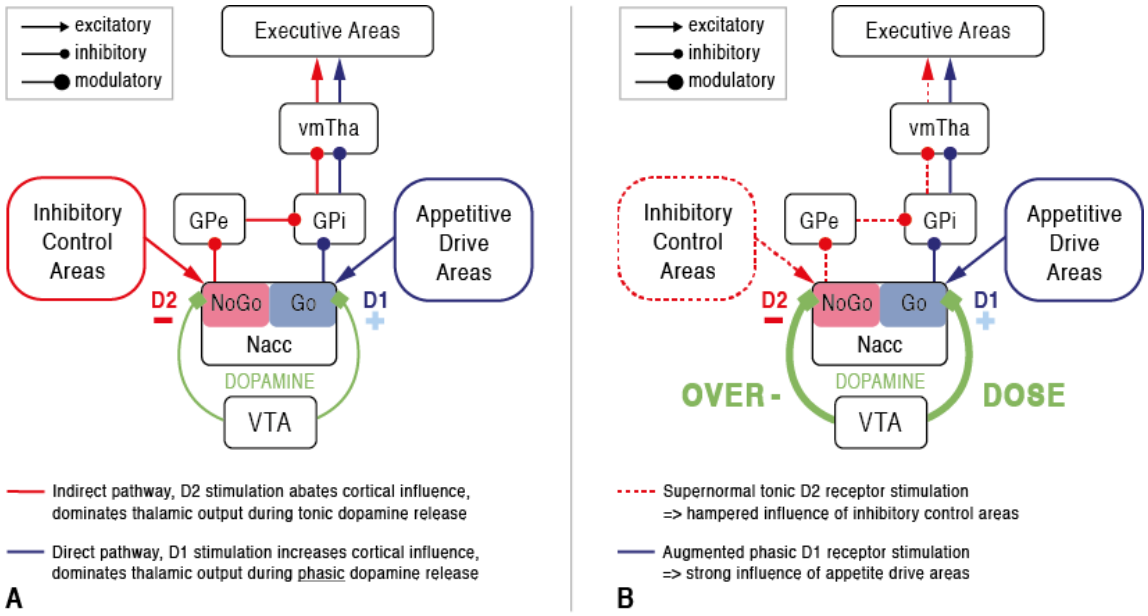



**Figure 1.7 Dopaminergic Effects in Healthy Patients and PD patients**

(A) Physiological effects of tonic and phasic dopamine release on cortical connections with the direct and indirect pathways of the basal ganglia in healthy subjects. In a majority of the patients with PD, dopaminergic depletion decreases tonic D2-receptor stimulation in the ventral striatum/Nacc.

(B) In a minority of susceptible patients, a constitutionally increased tonic dopamine level leads to relatively normal levels of tonic D2-receptor stimulation in the ventral striatum/Nacc. Dopamine agonists may further increase D2-receptor stimulation possibly leading to an 'overdose' situation, where a hampered engagement of top–down inhibitory control cortical areas and increased influence of bottom–up appetitive drive areas predispose to behavioral disturbances.

*Abbreviations: GPe, external globus pallidum; GPi, internal globus pallidum; Nacc, nucleus accumbens; vmTha, ventro-medial thalamus; VTA, ventral tegmental area. Adapted from (Cilia and van Eimeren, 2011)*

An alternate theory is a "Dopamine denervation" model: *De novo* (drug naive) patients seem to respond well, cognitively, to the introduction of L-dopa. In contrast, stable L-dopa medicated patients obtain no benefit. Furthermore, those patients already experiencing "on/off" (motor) fluctuations seem to be cognitively *impaired* by an acute L-dopa challenge (Kulisevsky J., 2000). This variation in response to L-dopa may be due to enhanced sensitivity to alterations in plasma concentrations of L-dopa – possibly due to reduced storage, reuptake and regulated release mechanisms. Chronic L-dopa administration might thereby lead to 'supersensitivity' of striatal neurons to a dopaminergic stimulus. L-dopa cognitive effects are therefore not straightforward and may have opposing effects both between individuals and within individuals on different tasks. These cognitive effects may also vary in an individual over time as a result of both disease progression (Williams-Gray et al., 2009) and receptor changes due to prolonged drug administration (Antonini et al., 1997).

### 1.5.6 The cognitive effects of Methylphenidate (MPH)

MPH is approved for the treatment of attention-deficit hyperactivity disorder (ADHD), where it is used to *reduce* impulsivity. It has also been demonstrated to reduce disinhibition in frontotemporal dementia (Rahman et al., 2006). In contrast, MPH has otherwise been used to increase motivation in the treatment of apathy (Marin et al., 1995; Galynker et al., 1997; Jansen et al., 2001; Hardy, 2009) and has become one of a handful of drugs taken as 'cognitive enhancers' by whose who are medically well (Husain and Mehta, 2011; Repantis et al., 2010; Swanson and Volkow, 2008). Whether MPH improves performance when endogenous neurotransmitter levels are optimal, or if its use is better restricted to those with abnormal baseline levels, remains unclear.

Much evidence of the cognitive effects of MPH comes from the ADHD literature, where speeding and attentional effects are common (Knights, 1969; Sprague et al., 1970). Improvements in higher level cognition (such as decision-making) are less certain (Adams, 1982; Advokat, 2010; DeVito et al., 2008a; Swanson et al., 2010). Persistent abnormal regional cerebral blood flow in the brains of ADHD patients treated with MPH (Schweitzer et al., 2004) supports the absence of higher level cognitive effect. Several studies, however, suggest that MPH *can* improve decision-making in ADHD. Children and adults showed improvements in executive function and neuropsychological test performance, respectively (Riordan et al., 1999). MPH led to a reduction in risk-prone betting, and improved performance, in the Cambridge Gambling Task (CGT) (DeVito et al., 2008b). MPH also improved time discrimination (Rubia et al., 2009) - highly relevant for the speeded tasks described in this thesis.

Such improvements in ADHD might be due to up-regulation of an hypofunctional anterior cingulate cortex (ACC (Bush et al., 2008)), an area implicated in risk-evaluation in healthy volunteers (Christopoulos et al., 2009). Similarly, MPH has been shown to restore the (previously hypoactive) ACC of cocaine addicted patients to normal levels of BOLD activity in a salient cognitive task (Goldstein et al., 2010). The normalised imaging findings were associated with reduced errors of commission and improved task accuracy. Other studies show that ADHD patients demonstrate similar slowing of SSRT to that seen in lesions of the right inferior frontal cortex. This impairment is also ameliorated by MPH (Aron et al., 2003). Whether these

effects are due to improvement of a system that is impaired at baseline, or can be replicated in healthy volunteers remains to be determined.

### 1.5.6.1 MPH effects upon decision-making in healthy human subjects

A review and meta-analysis of 46 studies of MPH looked for effects upon motivation, wakefulness, attention and vigilance (Repantis et al., 2010). It found no *consistent* evidence for any "neuroenhancing" effect of MPH. As in ADHD, beneficial effects of MPH are reported in both reaction-time and response inhibition tasks: "Low-level" effects such as speeding of simple reaction time are reported – particularly for more complex responses (Fitzpatrick et al., 1988; Naylor et al., 1985) - perhaps due to effects on attention (Camp-Bruno and Herting, 1994). MPH increases digit span but had no effect upon decision-making (Agay et al., 2010). However, performance improvement has been demonstrated in tasks sensitive to frontal lobe damage (Elliott et al., 1997). Go-trial reaction time was reduced by MPH in a stop-signal reaction time (SSRT) task (Eagle et al., 2007) without changes in the SSRT or error rate. However, an fMRI study using two versions of the stop-signal task found that MPH improved inhibitory performance (Pauls et al., 2012) in association with reduced activation of regions within the right inferior frontal gyrus/insula. An imaging study suggests that MPH exerts (dopaminergic) effects on the *speed of processing* of uncertainty but failed to demonstrate any influence over the choice outcome in decision-making tasks (Schlösser et al., 2009).

### 1.5.6.2 MPH effects upon reward learning in animals and humans demonstrate task-dependence and an inverted U-shaped relationship

This inconsistency in effects may reflect the existence of an optimal dopamine "level" for particular tasks. Rats demonstrated improved overall attention, in a 5 choice serial reaction time task, with methylphenidate but the highest dose also *increased* impulsivity (Navarra et al., 2008). In contrast, *reduced* impulsivity was found following MPH administration in a delayed reward task. There is also evidence of dose-and baseline performance-dependent effects in rats: In a stop-signal task, MPH led to both a reduction in the go-trial reaction time and differential effects dependent upon baseline SSRT (Eagle et al., 2007): MPH *decreased* SSRT in *slow* responders but *increased* SSRT in *fast* responders – consistent with the "optimal DA" level or "inverted U-shaped" hypothesis (Figure 1.6). Non-human primates demonstrate similar effects (Gamo et al., 2010). Optimal doses of MPH improved spatial working memory in monkeys whereas excessive doses did not. Dose-dependent effects are also found in oculomotor delayed response tasks sensitive to working memory, impulsivity, response accuracy, precision and attentional performance (Rajala et al., 2012). In humans, this inverted U-shape relationship between cognitive performance and dopaminergic activity in frontostriatal circuits has been investigated using [$^{11}$C]-raclopride labelled PET imaging (Clatworthy et al., 2009). Performance on a reversal-learning task was predicted by the MPH-induced change in D2/D3 receptor availability in the post-commisural caudate. Spatial working memory task performance related to similar changes in the ventral striatum. Reversal-learning performance was predicted by subject trait impulsivity (BIS-11 score): The most impulsive individuals benefitted most from the drug.

#### 1.5.6.3 MPH effects upon eye movements

When administered to boys with ADHD, MPH was found to reduce both pro- and anti-saccadic reaction times, error correction times and the proportion of direction errors in an anti-saccade task (Klein et al., 2002). A study using oculomotor tasks in ADHD patients found that MPH improved performance in both motor planning and response inhibition (O'Driscoll et al., 2005). Given the paradoxical effects of stimulant medications in ADHD (Robbins and Sahakian, 1979), these results must be interpreted with caution. No saccadic or other eye movement effects of MPH upon healthy volunteers are reported to date.

#### 1.5.6.4 Summary

Both L-dopa and MPH have been demonstrated to show task and subject dependent effects on rewarded behaviour. Some of these effects are dependent upon baseline performance and show an "inverted U-shape" relationship: Poor baseline performance is improved but optimal performance is worsened by drug administration. Both drugs have varying effects upon time estimation and reaction time, both of which are important in the tasks performed in the experiments described in chapters 5 and 6.

## 1.6 The effects of Age upon rewarded decision-making

Healthy aging brings about many changes in cognition (Cabeza et al., 2004) reflected in altered structure, function and biochemistry (Marschner et al., 2005; Alichniewicz et al., 2013) that generally cause slowing of cognitive performance (Der and Deary, 2006; Verhaeghen and Salthouse, 1997). Specific mechanisms of cognitive aging and their impacts upon impulsivity and decision-making are uncertain (Brown and Ridderinkhof, 2009; Deary et al., 2009; Mohr et al., 2010) but age-related decrements in performance on a variety of attention-related tasks, including sustained attention, selective attention, and inhibition tasks have been shown (Heuninckx et al., 2005; Mani et al., 2005; Wu and Hallett, 2005; Voelcker-Rehage and Alberts, 2007). These changes have led to the development of a "frontal aging hypothesis" (Isella et al., 2008), driven by dopaminergic (and serotonergic) changes in the aging brain accompanied by structural change in the striatum and prefrontal cortex (PFC, (Marschner et al., 2005)). Some experiments demonstrate that risk-taking behaviour in healthy volunteers changes with age (Deakin et al., 2004) and that the ability to make profitable choices declines in some older people (Denburg et al., 2005, 2007). Increased risk aversion can appear to specifically contribute to poorer decision-making (Boyle et al., 2012), but may otherwise reflect a more global cognitive decline (Albert and Duffy, 2012). Both increased risk *seeking* and risk *aversion* are found in older adults, depending upon the task design employed (Mather et al., 2012).

### 1.6.1 Age alters dopaminergic function in frontostriatal circuitry, leading to changes in reward-motivated behaviours

Theories of declining cognition implicate reduced dopaminergic activity in frontostriatal networks with age (Bäckman et al., 2006, 2010; Erixon-Lindroth et al., 2005; Kaasinen and Rinne, 2002; Kaasinen et al., 2000; Klostermann et al., 2012; Li et al., 2010). One proposed mechanism for the "rise and fall" in optimal decision making ability with age is that the development of dopaminergic frontal inhibitory control (particularly by the PFC) which occurs during

adolescence is selectively impaired by the aging process (Braver et al., 2001). Younger subjects tend to outperform older ones in tasks requiring a high degree of frontal cortical activity. However, there is evidence that older subjects recruit other brain regions to replace these age-related frontal deficiencies (Park et al., 2001). Interpretation is not straightforward: younger subjects may use different strengths (e.g. learning and memory) to older subjects (who may more accurately represent valence) in order to achieve similar task outcomes (Wood et al., 2005). Apparent decision-making differences may be attributed changes in processing speed and memory rather than changes in risk/reward sensitivity (Henninger et al., 2010) and some authors report age-related changes in bias-susceptibility rather than decision-making ability *per se* (Kovalchik et al., 2005).

In a study of probabilistic reward-based stimulus association tasks, the older group showed poorer overall acquisition and impaired reversal learning (Weiler et al., 2008). Older subjects also required greater reward magnitudes to exhibit steep learning curves. There is increasing evidence that specific frontal D2 and D3 dopaminergic degeneration leads to these changes in reward sensitivity (Volkow et al., 1996, 2000; Kaasinen et al., 2000). Functional imaging during a slot machine task demonstrated a correlation between midbrain dopamine synthesis and reward-related pre-frontal activity (Dreher et al., 2008). There was an age-related change in the direction of the relationship, from a positive to a negative correlation. Furthermore, dopamine (L-dopa) has been shown to restore reward prediction errors to youthful levels in healthy older volunteers (Chowdhury et al., 2013). Recent experiments suggest that there are age-related differences in fronto-striatal representations of prediction errors as opposed to reward outcome (Samanez-Larkin et al., 2014).

There is also evidence for specific *subcortical* differences in aging and reward. Using a Go/Nogo task, correlations between MRI volumetric measures in the caudate and putamen/globus pallidus (PGp) and age have been demonstrated (Langenecker et al., 2007). Multiple task performance measures correlated with activation in the left PGp, thereby implicating this structure in mediating age related task performance differences. Similarly, in another response inhibition task (Coxon et al., 2012), functional anisotropy demonstrated that cortico-subthalamic (preSMA-STN) connection strength predicted stopping performance, thereby linking an age-related decline in in inhibitory control with structural decline in STN projections.

### 1.6.2 Are older people more or less impulsive or just apathetic?

Poorer IGT and antisaccade task performance suggests that frontostriatal networks work less effectively in older people (Olincy et al., 1997; Butler et al., 1999; Fein et al., 2007) and implicates aging of this system (Raemaekers et al., 2006) in the impaired inhibition of action (Sweeney et al., 2001). Conversely, improving antisaccade task performance is attributed to frontal lobe development during adolescence (Munoz et al., 1998). As a result, older adults are more susceptible to oculomotor capture and exhibit deficient selective suppression of the responses captured by the task irrelevant distracters in a saccadic task (Ridderinkhof and Wijnen, 2011). These changes in frontal executive function would lead us to expect impulsivity to increase with age. However, a study in older people found that "stimulation seeking" *decreased* with age

(Giambra et al., 1992). Age-related reductions in delay discounting have also been related to lower ventral striatal activations to immediate reward using fMRI (Eppinger et al., 2012).

Reaction time studies demonstrate that older subjects have a preference for accuracy over speed (Rabbitt, 1979; Welford, 1988; Smith and Brewer, 1995). Behavioural task success requires anticipation of actions that need to be executed - a capacity that specifically appears to be negatively affected by aging (Falkenstein et al., 2006; Roggeveen et al., 2007; Sterr and Dean, 2008). This may be, in part, due to changes in motivation. Apathy is common in aging and manifests as lack of interest and initiative, and emotional blunting (Ishii et al., 2009; Brodaty et al., 2010; Esposito et al., 2014). Nevertheless, there is an association with cognitive impairment (Starkstein et al., 2006; Onyike et al., 2007) which suggests that apathy should not always be considered a 'normal' part of aging. Moreover, a recent study suggests that, rather than apathy, age may cause a specific deficit in the acquisition of goal-directed action (Wit et al., 2014).

### 1.6.3 Age affects saccadic performance

Though robust compared to other motor measures (Pratt et al., 2006), SRT increases above 50 years of age (Irving et al., 2006; Pitt and Rawles, 2009) with an associated increase in variability in latency (Abel and Douglas, 2007), reduced velocity and accuracy (Schik et al., 2000; Sharpe and Zackon, 2009). Older participants are more susceptible to saccade disruption than young adults (Gottlob et al., 2007) and exhibit more hypometric and multi-step saccades (Litvinova et al., 2011), rendering their responses less reliable. Voluntary (as opposed to reflexive) saccades seem particularly vulnerable to the effects of age (Peltsch et al., 2011). A "global slowing" phenomenon (Golob et al., 2009) is manifest in differences in "gap" effect saccade latency benefit (Pratt et al., 1997): Though the *absolute* benefit is reduced in older people, it is of a similar *proportion* of the saccade latency when compared with younger individuals suggesting that though overall processing is slowed, the fundamental mechanisms of saccade production/inhibition are intact.

In Chapter 2, I introduce a novel, rewarded oculomotor task in which subjects must make speeded oculomotor decisions under risk for reward. I compare the performance of young healthy volunteers with an older group. This older group later serves as an age-matched control group for patients with Parkinson's Disease.

## 1.7 Parkinson's Disease is associated with apathy and impulsivity

Parkinson's disease (PD) is associated with degeneration of the dopaminergic neurons in the substantia nigra *pars compacta* (SNc) and the surrounding area (Braak et al., 2003). This leads to a triad of movement abnormalities (tremor, rigidity and bradykinesia (Parkinson, 2002)) and various effects upon cognition and mood (Aarsland et al., 2009a, 2009b; Burn et al., 2014; Weintraub and Burn, 2011). Parkinson's Disease (PD) is associated with both apathy (Starkstein et al., 1992; Isella et al., 2002; Robert et al., 2002; Pluck and Brown, 2002; Dujardin et al., 2007) and impulsivity (Nombela et al., 2014; Voon et al., 2011a; Weintraub and Nirenberg, 2012; Weintraub et al., 2010). Dopaminergic dysfunction has been proposed as the origin of this aberrant motivated behaviour (Volkmann et al., 2010; Voon et al., 2011d). In some PD patients, impulse control disorders develop, including pathological gambling (Avanzi et al., 2006; Driver-Dunckley et al., 2003; Gallagher et al., 2007; Molina et al., 2000; Voon et al., 2011a; Weintraub et al., 2010). This propensity may reflect a gradient pattern of dorso-ventral striatal degeneration and/or differential dopaminergic treatment effects upon those structures (Lawrence et al., 2013; Macdonald and Monchi, 2011; Steeves et al., 2009). It is proposed that impulsivity may reflect *excessive* dopaminergic transmission while apathy is reflective of *reduced* corticostriatal dopaminergic activity. The situation is clearly more complex/multidimensional than this (Sinha et al., 2013a) but it is a useful starting point. Parkinson's is a useful model for the development of the ideas in this thesis for a number of reasons:

1. Parkinson's patients often demonstrate apathy (Oguru et al., 2010).
2. Some PD patients may otherwise develop problems with impulse control (Voon et al., 2011c), leading to impulse control disorders (ICDs)
3. PD disrupts the corticostriatal networks which are implicated in the pathophysiology of both of these constructs (Balleine et al., 2007).
4. "Orbitofrontal" and "cingulate" striatofrontal loops and the mesolimbic dopaminergic system that modulates their function are implicated in motivation and sensitivity to reinforcement in animals. Parkinson's disease (PD) provides a model to assess the implications of damage to these structures in humans in humans (Czernecki et al., 2008) .

### 1.7.1 Disordered Decision-Making occurs in PD

Cognitive deficits are a recognised consequence of PD (Burn et al., 2014), even early in the disease and in younger patients (Aarsland et al., 2003; Collins, 1998; Lewis et al., 2003). PD causes similar disorders of executive function to frontal lobe brain lesions (Rogers et al., 1998; Taylor et al., 1986). Executive dysfunction in non-demented PD patients may impair decision-making and/or change patients' risk sensitivity (Robbins and Cools, 2014). PD patients are less able to make profitable choices in the Iowa Gambling Task (Mimura et al., 2006), and are impaired on the Game of Dice Task, another measure of decision-making under risk (Brand et al., 2004).

Both PD and the drugs used in its treatment may contribute to impulsive behaviour. A screen for ICDs, impulsivity and compulsive behaviours in a large cohort of PD patients *before*

initiating dopamine replacement therapy showed that a significant proportion of PD patients demonstrated ICDs (Antonini et al., 2011). These patients had higher Attentional Impulsiveness (AI) compared to ICD subjects (without PD) on the BIS-11. In treated and untreated PD patients, those with ICDs demonstrated found higher "motor impulsiveness" and total BIS-11 scores (Bentivoglio et al., 2013). There was also a trend toward worsened performance in the PD-ICD group on neuropsychological tasks sensitive to frontal lobe dysfunction. However, some evidence suggests that IGT performance deficits emerge only *following* treatment with dopamine agonists (Poletti et al., 2010). Subsequent overstimulation of orbito-fronto-striatal networks may disrupt reward processing and harm avoidance (and hence decision-making) such that impulse control disorders occur (Brand et al., 2004, 2005).

Impulsiveness in PD patients (without *diagnosed* ICDs) has been attributed to four principal factors (Nombela et al., 2014): 1. Tests of response conflict, interference and self-assessment of impulsive behaviours on the Barratt Impulsivity Scale; 2. Tests of motor inhibitory control, and the self-report behavioural approach system; 3. Time estimation and delay aversion; 4. Reflection in hypothetical scenarios including temporal discounting.

### 1.7.2 Dopaminergic effects upon decision-making in PD relate to a dorso-ventral gradient of degeneration

Cognitive effects of PD have been shown to relate to altered dopaminergic function within basal ganglia structures and frontal cortex (Rinne et al., 2000; Sawamoto et al., 2008). Investigators have shown both 1) improvement in *some* cognitively demanding tasks and 2) impaired task performance in *other* kinds of test when comparing PD patients on and off dopaminergic medication (Cools et al., 2003). In particular, it seems that DA *strengthens* associations between reward processing and novelty seeking but *disrupts* the links between punishment processing and harm avoidance (Frank et al., 2004; Bodi et al., 2009). The ventral striatum is critical in effecting the impulsive and apathetic behaviours due to high and low dopaminergic levels (Dagher and Robbins, 2009) (Table 1.2). In early PD, there is greater dopaminergic loss in the dorsal striatum than in ventral areas (Kish et al., 1988). Clinically effective dopaminergic therapy for the dorsal striatum may therefore "overtreat" the relatively intact ventral striatum and cause cognitive side effects (Gotham et al., 1988). This may be due to sensitized D2/D3 receptors in the striatum (Evans et al., 2006; Steeves et al., 2009) and/or decreased dopamine transporter availability (Cilia et al., 2010, 2011). PD patients with Impulse Control Disorders (ICD) seem to overvalue immediate rewards despite intact reward learning (Housden et al., 2010). Functional imaging studies suggest that this is due to altered striatal activation and corticostriatal connectivity (Rao et al., 2010; Voon et al., 2010).

In Chapter 7, I investigate the oculomotor decision making in patients with PD with and without ICD.

| *Cortical Origin of the Cortico-Striatal Loop* | *Striatal Region* | *Effect of Low Dopamine* | *Effect of High Dopamine* |
|---|---|---|---|
| Primary Motor | putamen | bradykinesia, clumsiness | dyskinesia |
| Accessory Motor | rostral putamen | Akinesia | stereotypies, tics |
| **Limbic** | **ventral striatum** | **"Parkinsonian personality," mental rigidity, neophobia** | **"addictive personality," impulsivity, novelty seeking, impaired reversal learning** |
| Prefrontal | caudate | Dysexecutive syndrome, impaired planning, working memory and cognitive flexibility | Compulsive disorders, punding |

**Table 1.2 Possible Site of Striatal Dopamine Dysfunction Causing Different Motor and Cognitive Symptoms in Parkinson's Disease**

(This model ignores cortical dopaminergic dysfunction in PD, for simplicity.)

*Adapted from (Dagher and Robbins, 2009).*

### 1.7.3 Dopaminergic agents increase risk taking in PD

Treatment with dopamine agonists (DAg) is the main risk factor for impulse control disorders (ICDs) in PD (Driver-Dunckley et al., 2003; Grosset et al., 2006; Voon et al., 2006; Weintraub, 2006). Pramipexole (a DAg) causes altered orbitofrontal fMRI BOLD activity in association with increased risk taking (van Eimeren et al., 2009). Differential effects of apomorphine (a DAg) on corticobasal ganglia circuitry have been demonstrated in patients with PD with and without ICDs (van Eimeren et al., 2010). $H_2{}^{15}O$ PET during a card selection game with probabilistic feedback performed both on and off medication found that the direction of change in brain activity differed in lateral OFC, rostral cingulate, amygdala and external pallidum. DAg *reduced* activity in PD gamblers whereas DAg *increased* activity in the same areas in PD controls.

L-dopa therapy may also influence ICD development independently (Weintraub et al., 2010) but this is less reliably demonstrated (Grosset et al., 2011). For example, withdrawal of L-dopa impaired performance on tests previously shown to be sensitive to frontal lobe dysfunction (Lange et al., 1992) but the drug worsened rewarded decision making in the Cambridge Gambling Task (CGT) (Torta et al., 2009). PD patients were unable to choose an optimal betting strategy and were impulsive in their choices relative to the control group. There was a detrimental, dose-dependent, effect of dopaminergic drugs including L-dopa. This is in contrast to other tasks, for example a probabilistic learning task, in which dopaminergic medications improved (previously impaired) PD patients' abilities to predict stimulus-action-reward relations (van Wouwe et al., 2012).

### 1.7.4 Parkinson's Disease has effects upon saccades that reflect cognition

PD causes hypometric, slow saccades with long onset latencies (Corin et al., 1972; DeJong and Jones, 1971; Jones and DeJong, 1971; Shibasaki et al., 1979; Teräväinen and Calne, 1980; Shimizu et al., 1981; White et al., 1983; Vidailhet et al., 1994; Jankovic, 2008). *Reflexive* saccades are relatively spared from impairment (White et al., 1983; Rascol et al., 1989; Vidailhet et al., 1994; Briand et al., 1999), but there are exceptions that also demonstrate increased latency (Bronstein and Kennard, 1985; Shibasaki et al., 1979). Latencies correlate with (diminished) executive function rather than motor severity (Perneczky et al., 2011). In reports of oculomotor prepotent response inhibition, latencies of antisaccades (AS) are increased and PD patients commit more pro-saccadic errors (Briand et al., 1999; Chan et al., 2005; Kitagawa et al., 1994; Lueck et al., 1990; White et al., 1983).

With regard to anticipatory responding, PD patients made more 'express saccades' of latency 90-140ms in one study (Chan et al., 2005). However, another found that patients were *less* likely to make *anticipatory* saccades (Bronstein and Kennard, 1985). The earlier finding was thought to be due to their over-reliance on visual input. In a study of manual and saccadic responses, the authors concluded that, though *capable* of predictive hand and eye movements, PD patients tend to avoid them due to greater inaccuracy (Crawford et al., 1989). Motivational incentives have been shown to improve antisaccade performance to a similar degree in PD patients, age

matched controls and younger patients, despite the PD patients having relatively poor baseline performance (Harsay et al., 2010).

### 1.7.5 Summary

In Parkinson's disease, both the disease and its treatment affect rewarded decision-making. Degeneration along a dorsoventral gradient in the striatum may partly explain these contributions, which are both task and dose dependent. Correlations between saccadic performance and executive function in PD suggest that oculomotor performance is independent of motor deterioration. This is explored in Chapter 7, where PD patients with and without ICDs are compared with pathological gamblers and age matched controls.

## 1.8 Pathological Gambling in otherwise healthy people may result from different mechanisms.

Pathological Gambling (PG) is recognised as a problem for both individuals and society. Studies demonstrate a lifetime prevalence of up to 2% (Cox et al., 2005; Welte et al., 2002). Diminished cognitive control and increased impulsivity are present in problem gamblers compared to healthy controls (Goudriaan et al., 2014). Increased impulsivity is demonstrated on measures of self-report such as the BIS-11 and Eysenck's Impulsiveness Questionnaire (Eysenck et al., 1985) and in behavioural measures such as delay discounting, response inhibition and cognitive interference tasks (Goudriaan et al., 2004; Verdejo-García et al., 2008; van Holst et al., 2010). However, research to date has failed to explore the differential effects of functional and dysfunctional impulsivity in gambling (Maccallum et al., 2007). Furthermore, PG has been otherwise conceived as a primary problem with addiction (Clark, 2010). This allies the pathology with that of substance use disorders where impulsivity is also found to be important (Leeman and Potenza, 2012) but also suggests that there may be different mechanisms for the impulse control disorder than in PD-ICD.

Dopaminergic activity contributes to the rewarding effects of addictive substances (Schultz, 2011), gambling behaviours (Campbell-Meiklejohn et al., 2011) and impulsivity (Buckholtz et al., 2010). Proposed biochemical dysfunctions in PG implicate altered responses to dopaminergic activity in the ventral striatum (Linnet et al., 2011, 2012). Such findings support the hypothesis of a "reward deficiency syndrome" wherein gamblers persistently seek reward due to a tonically underactive dopaminergic reward system (Blum et al., 2000) which is *also* under-responsive to rewards when obtained (Reuter et al., 2005). This contrasts to theories of ICD in PD, where *excessive* dopaminergic states (with overtreatment of a relatively *spared* ventral striatum) are blamed for impulsive decision making (MacDonald and Monchi, 2011; Leeman and Potenza, 2012; Vriend et al., 2014).

### 1.8.1 Cognitive control and impulsivity in Pathological Gambling

Only seven specific neuropsychological experimental reports involving gamblers were found by a 2004 review (Goudriaan et al., 2004). Gamblers show poor performance on simple tests like the Wisconsin card sorting task, embedded figures task and Porteus mazes (Rugle and

Melamed, 1993), suggesting deficits in planning and attention. Experiments since that review have demonstrated that pathological gamblers performed poorly in tasks requiring inhibition, time estimation, cognitive flexibility and planning (Goudriaan et al., 2006a). As a result of these deficits, gamblers exhibit poor decision-making: Delay discounting, probability discounting and decision-making impairment on the IGT are consistently found to be impaired in PG (Petry, 2001; Cavedini et al., 2002; Alessi and Petry, 2003; Goudriaan et al., 2005, 2006b; Kertzman et al., 2011; Wiehler and Peters, 2014).

Behavioural investigation of pathological gamblers *under time pressure* has focused on tasks of prepotent response inhibition, such as stop-signal reaction time (Lipszyc and Schachar, 2010) and Go/Nogo tasks (Kertzman et al., 2008): A (poorly controlled) study found that pathological gamblers' performance was impaired versus other groups in a stop-signal reaction time (SSRT) task (Odlaug et al., 2011). Gamblers had slower response latencies on "go" trials and made more errors on a cognitive flexibility task. The major confound in this study was that subjects in the pathological gambling group were significantly older than controls. This may account for some (or all) of the differences found. A better controlled study using both SSRT and delay-discounting tasks found greater delay-discounting in all gamblers, but SSRT impairment only in the most severely affected (Brevers et al., 2012). Another study found no relationship between the impaired IGT performance of gamblers and their Stroop or Go/Nogo performance, suggesting that PG is not due to failure of inhibition (Kertzman et al., 2011).

### 1.8.2 Pathological Gambling has both corticostriatal lesion and imaging correlates

Similarities between IGT performance in PG groups and those with vmPFC lesions suggest a role for pathophysiology in this brain area in the development of PG (Cavedini et al., 2002). This is supported by imaging and lesion studies in patients: Substance abusers with and without gambling problems were compared with healthy volunteers performing the IGT. Reduced fMRI BOLD activity was found in the vmPFC, right frontopolar and superior frontal cortex during decision-making (Tanabe et al., 2007). Similarly, impaired performance by gamblers in the Game of Dice Task is suggestive of a role for the dorsolateral PFC (DLPFC) (Brand et al., 2005). These frontal areas connect to striatal regions as part of limbic/decision-making loops. An fMRI study using a guessing game found that gamblers' reduced ventral striatal and ventromedial prefrontal activation negatively correlated with gambling severity (Reuter et al., 2005). Imaging in healthy volunteers also suggests that these brain areas (in addition to the PFC) are important in modulating loss aversion in decision-making under risk (Tom et al., 2007).

To our knowledge, no one has previously used saccadic tasks to study problem gamblers. Furthermore, there is a lack of reports of fundamental psychophysical measures (such as a reaction time) in this group. In Chapter 7, oculomotor tasks are used to compare decision making in 3 patient groups: PD patients, PD patients with ICD and pathological gamblers. These subjects are also compared with age-matched control groups consisting of healthy volunteers.

## 1.9 Summary & Thesis Synopsis

In this thesis I will develop the hypothesis that motivated decision-making in humans can successfully be studied using rewarded oculomotor tasks. Furthermore, disruption of the limbic, corticobasal ganglia circuitry that causes aberrant rewarded decision-making might be interrogated successfully in this way.

I first investigate the effects of age and the consequent dopaminergic, frontal degeneration that might impact on rewarded oculomotor decision-making (Chapter 2). In Chapter 3, I explore additional oculomotor tasks and correlations between task performance and established, questionnaire-based self-report measures of impulsivity. Chapter 4 describes experiments involving a patient with focal lesions causing apathy and the effects of therapy with dopaminergic medication upon oculomotor task performance. Experimental chapters 5 & 6 concern the administration of drugs known to modulate dopaminergic transmission and their effects on oculomotor decision making in healthy volunteers. Chapter 7 reports the results of investigation of oculomotor task performance in patients with Parkinson's disease, with and without impulse control disorders, and pathological gamblers.

# 2. Rapid decision making under uncertainty: The effects of age

## 2.1 Introduction

This chapter introduces a novel behavioural paradigm designed to study decision-making under risk. It also describes exploration of the effect of subject age upon the task.

### 2.1.1 Task Design

The study of decision-making has become the focus of intense research efforts in cognitive neuroscience. However, it is appreciated that there might be limitations associated with existing naturalistic tasks used to identify abnormal decision-making (Schonberg et al., 2011). For example, delay discounting (Bickel et al., 1999) or gambling tasks (Bechara et al., 1998; Clark et al., 2008; Murphy et al., 2009) have been extraordinarily useful in identifying departures from normal behaviour. However, they may encourage probabilistic fallacies or may not permit behaviour to be dissected easily into its contributory components (Aragues et al., 2011). They also allow participants to reflect upon the decision and consider possible outcomes without time pressure or urgency.

Conversely, impulsive behaviour in pathological groups is often characterised by rapid decision-making under risk (Moeller et al., 2001). Impulsivity may be conceptualised as the willingness to decide before all the required information is available. Some existing tests probe this in patient groups, albeit for decisions made in the order of many seconds rather than in milliseconds e.g. (Clark et al., 2006). But even in healthy humans, under certain circumstances, early decisions can carry a survival advantage, as when deciding quickly might be life saving even if associated with a risk of making the wrong choice. Such an ability to make rapid decisions and negotiate risk early might be termed functionally impulsive cf. (Dickman, 1990). However, in other scenarios a "wait and see" approach is better, particularly if early decisions repeatedly lead to poor outcomes.

We designed a new paradigm – the "traffic light task" – deliberately to provide a measure of decision-making under time pressure. The task encourages functionally useful anticipation but also punishes erroneous decisions made too early. Saccades were used as our response measure (see Introduction, Section 1.2): Subjects were asked to make horizontal eye movements *as quickly as possible* in response to a green traffic light, "Go!" signal. Risk was introduced by varying the amber light duration and so that the green, "Go!" signal was not predictable. The rules encouraged participants to make functional anticipatory responses by disproportionately rewarding fast decisions that led to saccades soon after the "Go!" signal. However, saccades made too soon, which were before "Go!" onset, were punished. Ideal performance incorporated fast reaction times based upon an anticipatory strategy. Individuals performed badly if they were either persistently too early (despite the negative feedback) or too slow.

### 2.1.2 Age Effects

Traffic Light Task performance might vary with age due to changes in saccadic reaction time (SRT), reward sensitivity (or risk aversion) or both. Ideally, these effects might be dissociable from the saccadic distributions produced. Slower SRTs would cause a rightward shift in the

reactive response distribution, whereas reward insensitivity should reduce anticipatory responding.

Risk taking behaviour in healthy volunteers changes with age (Deakin et al., 2004) and the ability to make profitable choices declines in some older people (Denburg et al., 2005, 2007). This risk aversion appears to contribute to poorer decision-making (Boyle et al., 2012), but may, in fact, reflect a more global cognitive decline (Albert and Duffy, 2012). Indeed both increased risk *seeking* and increased risk *aversion* are found in older adults, dependent upon the task design (Mather et al., 2012). However, these effects can otherwise be attributed to individual differences in processing speed and memory (Henninger et al., 2010) rather than changes in risk/reward sensitivity.

With respect to eye movements, this "global slowing" phenomenon is manifest in differences in "gap" effect saccade latency benefit. Though the *absolute* benefit is reduced in older people, it is of a similar proportion of the saccade latency when compared with younger individuals (Pratt et al., 1997) suggesting that though overall processing is slowed, the fundamental mechanisms of saccade production/inhibition are intact.

Though robust compared to other motor measures (Pratt et al., 2006) SRT increases slightly, and gradually, above 50 years of age (Irving et al., 2006; Pitt and Rawles, 2009) with an associated increase in variability in latency (Abel and Douglas, 2007), reduced velocity and accuracy (Schik et al., 2000; Sharpe and Zackon, 2009). Older participants are also more susceptible to saccade disruption than young adults (Gottlob et al., 2007) and exhibit more hypometric and multi-step saccades (Litvinova et al., 2011), rendering their responses less reliable. Voluntary (as opposed to reflexive) saccades seem particularly vulnerable to the effects of age (Peltsch et al., 2011). Declining antisaccade task performance (Butler et al., 1999; Olincy et al., 1997) implicates an aging fronto-striatal system (Raemaekers et al., 2006) in the impaired inhibition of action (Sweeney et al., 2001). This mirrors the improvement in antisaccade task performance attributed to frontal lobe development during adolescence (Munoz et al., 1998) and fits with general theories of declining cognition in association with reduced dopaminergic activity in frontostriatal networks with age (Bäckman et al., 2006, 2010; Erixon-Lindroth et al., 2005; Kaasinen and Rinne, 2002; Kaasinen et al., 2000; Klostermann et al., 2012; Li et al., 2010).

Do older, slower subjects display similar task responses to young controls in the Traffic Light Task? Does lack of reward sensitivity or inaccuracy/variability in timing lead to a risk-averse avoidance of anticipatory responding? Alternatively, might impaired inhibition lead to increased anticipation in spite of a higher error rate? I sought to answer these questions using our newly designed traffic light task.

## 2.2 Methods

Young subjects consisted of 45 healthy volunteers (mean age = 20; 22 females) recruited by email and from the University College London Psychology Subject Pool (Soma Systems). Older participants comprised 15 healthy volunteers (mean age = 64; 9 female) recruited by email/telephone/posters in local libraries and adult education centres. All subjects were naive to eye movement tasks generally and to our task in particular. They were also screened for neurological or psychiatric conditions by direct questioning of known past medical history. Ethical approval was sought and obtained from the local committee.

### 2.2.1 Traffic Light Task (Figure 2.1)

In the main experimental task, participants were told that their main aim was to win as much money as possible. They were asked to make rapid eye movements from a 'traffic light' (coloured disc 3 degrees in diameter) to a target cross (3x3 degrees), both presented on a computer monitor (60cm from the chin rest/plane of the eye). The traffic light and target were 10 degrees either side of the screen center (Figure 2.1). Subjects were requested to fixate the traffic light stimulus while it turned from red (duration 1000 ms) through amber to green. They were asked to make their 20 degree saccade to the target cross *as quickly as possible* and as soon after the GO signal as possible. They had a maximum of 1000ms in which to respond.

The reward ($R$) for a successful saccade was calculated by an exponentially decaying discounting function in the form:

$$R = ae^{-\left(\frac{t-t_0}{k_1}\right)}$$

Where $a$ = 150, $k_1$=100 and $t$ represents the saccade onset time relative to green onset ($t_0$, milliseconds).

This steep discounting function (Figure 2.1C) generated disproportionately high rewards for short saccadic reaction times (SRTs). Saccades with latencies of 400ms after green light onset were rewarded with only 2.8 pence; SRT=300ms made 7.5 pence while SRT=200ms generated 20.3 pence. Saccades with shorter latencies than this were far more highly rewarded: a response with SRT=100ms made 55.2 pence and 50ms led to a reward of 91.0 pence. But note that to make these high rewards, subjects would have to anticipate green light onset because saccades typically take ~200 ms to programme (White et al., 1962). In other words, they would have to make a decision – take a risk – to programme a saccade *before* the onset of the GO! signal. Such saccades, with latency <200ms and reward >20 pence were signalled by a reinforcing "Kerching!" sound whereas slower correct responses resulted in a simple "Ping".

Saccades that were actually made before the green light incurred a small, fixed penalty of 10 pence. Error trials were accompanied by an unpleasant audible beep and a visual warning, 'STOP POLICE! Fine £0.10.'.

The timing of the GO signal (green light) onset was not absolutely predictable from trial to trial. Instead, the duration of the amber light (Figure 2.1B) was randomly selected on each trial from a normal distribution (mean 750ms, SD 125ms). To perform optimally, participants therefore needed to make as many rewarded anticipations as possible, while keeping errors to a minimum. They had to make a choice of whether to stay (wait longer) or go and risk a small penalty versus the possibility of a large reward.

On gaze arriving at the target cross (fixation tolerance 2°), subjects received both aural and visual feedback on their performance. They were shown the reward (in pence) on the trial just completed, and a running total beneath (in pounds). The target cross was then replaced by a red light (circle) and a target cross now appeared on the opposite side of the screen to begin the next trial. To perform optimally, subjects should therefore make as many anticipations as possible, but as few errors as possible. Subjects performed ten blocks of fifty trials, the first trial in each block started from a left sided stimulus (rightward saccade) and then alternated.

Subjects sat on a height adjustable chair under a height adjustable table in a dimly lit room. They placed their forehead on a rack mounted EyeLink 1000 infra-red video-based eye tracker (SR Research Ltd, Ontario, Canada) recording eye position at 1000 Hz. A chin rest was then adjusted to provide comfortable support. The task stimuli were displayed on a flat-screened 22" CRT monitor (Dell P1230, 507.7mm viewable, displaying 1024x768 pixels, refresh rate 150 Hz) at 60cm from the vertical plane of the subject's eye. Eye position was calibrated to a 9-point rectangular matrix before testing began.

The task stimuli were programmed in C/C++ and run on a personal computer ((PC), Dell Optiplex 755 running Windows XP SP3). The eye tracker was controlled by a separate PC (Dell Precision 380) networked to the stimulus/display PC. This allowed real-time task feedback responses to eye movements. Eye position and pupil area data were acquired in real time and exported into Matlab R2008a (The Mathworks, Massachusetts, USA) for analysis.

Eye position data was used to detect fixations during each trial. Saccadic latencies were calculated from the onset of the second fixation in each trial (i.e. arrival at target) and referenced to time stamps produced by the onset of the traffic light stimuli. Saccades made in advance of the amber light were excluded from the analysis. All saccades made from amber onset until 1000ms following green onset were included in the analysis. Though blink errors were unavoidably included in the real-time feedback to the participant, blink trials were excluded from our *post hoc* analysis.

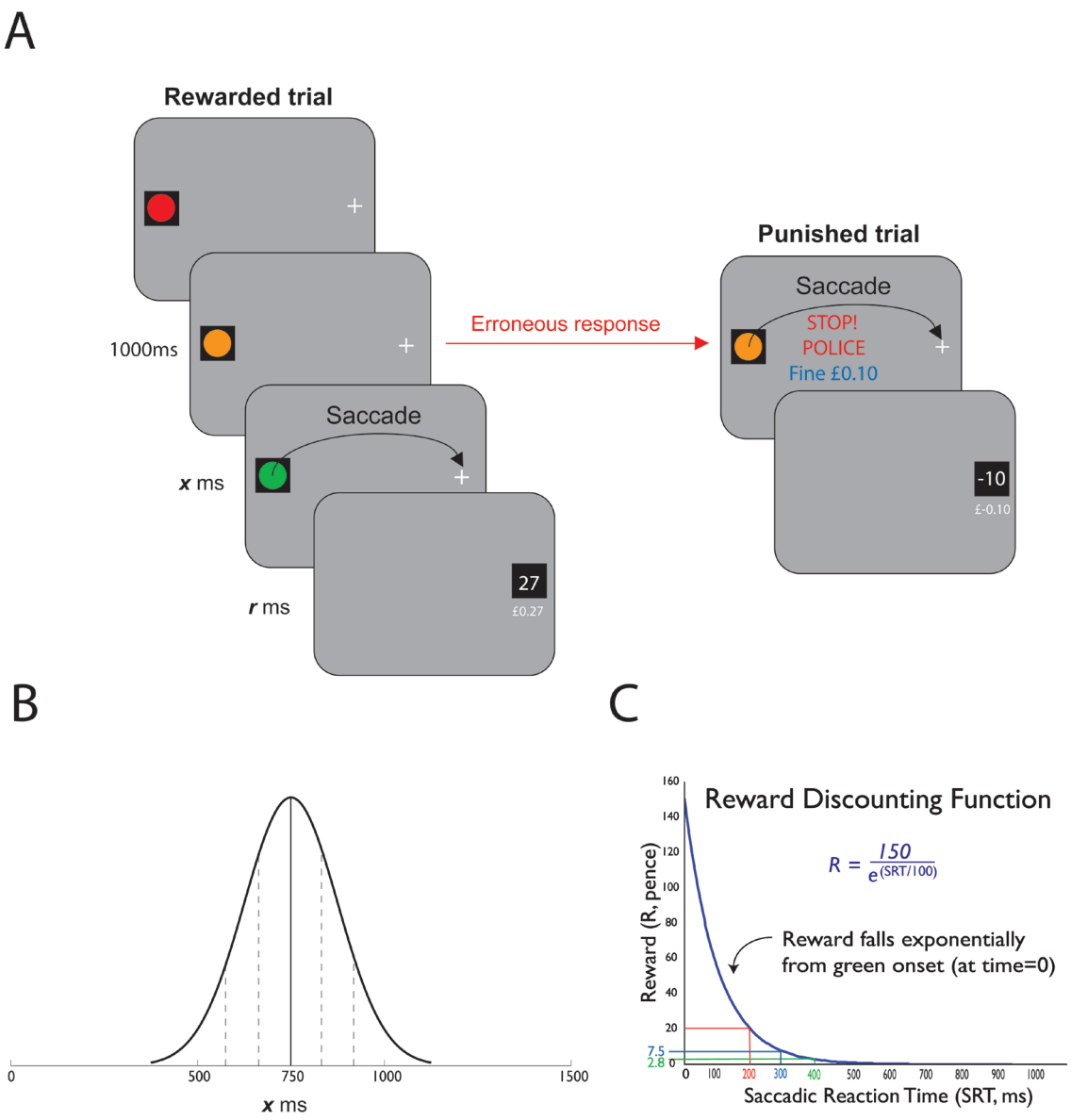



**Figure 2.1 The Traffic Light Task**

**A** Subjects were instructed to move their eyes as quickly as possible from a traffic light stimulus to a target cross. Saccades made after the green light were rewarded but those executed before the green light incurred a small penalty. **B** Amber duration was randomly selected on each trial from a normal distribution (mean 750ms, SD 125ms). **C** Reward was computed by a steep discounting function of saccadic reaction time. The biggest reward was for saccades that coincided with green light onset, but such saccades would have to been programmed before the green light.

### 2.2.2 Control saccadic reaction time (SRT) task (Figure 2.2)

In addition to the traffic lights task, young participants were also tested on a control, non-rewarded saccadic reaction time (SRT) task (Figure 2.2). In this paradigm, the red light was followed immediately by green, with no amber light between these. Red light duration varied between 500-1000ms (rectangular probability distribution, mean 750ms). Data acquisition was as above. This task allowed us to obtain response distributions for 'reactive' saccades – those programmed in response to green onset, without any need to anticipate the GO signal.

## 2.3 Results

### 2.3.1 Saccadic distributions in young controls

Typical saccadic reaction time tasks produce saccadic latency distributions with a single 'quasi-normal' distribution that is positively skewed. Since the skew can be removed by re-plotting on a reciprocal time axis, the distribution is given the name 'recinormal' (Carpenter and Williams, 1995). Performance on the control SRT task produced such a distribution (Figure 2.3A) with a mean reaction time of 335ms (SD 148ms) and median of 300ms for young volunteers.

On the traffic light task, however, the overall distribution saccades plotted with respect to green onset was bimodal (Figure 2.3B), consisting of two distinct distributions: a 'late' distribution which corresponded well to the distribution of saccades on the SRT task (cf. Figure 2.3B) and an 'early' distribution of saccades. Plotting saccadic distributions as a function of amber duration revealed an important feature of performance: as amber duration increased, the frequency of early saccades increased while that of late saccades reduced (Figure 2.4). Note also that the peak latency of the later distribution remained invariant across amber durations.

Given that saccades take ~200 ms to programme and execute (White et al., 1962), the early population of saccades might be considered anticipatory in nature while the later population (which matches well with the distribution in the SRT task) might be considered reactive – responses triggered by the onset of the green light. However, for any given saccade it is not possible definitively to determine whether it arose from the early or late population of responses. We therefore modelled our data to enable us to choose an appropriate 'cut-off' time for counting the number of 'anticipatory' responses.

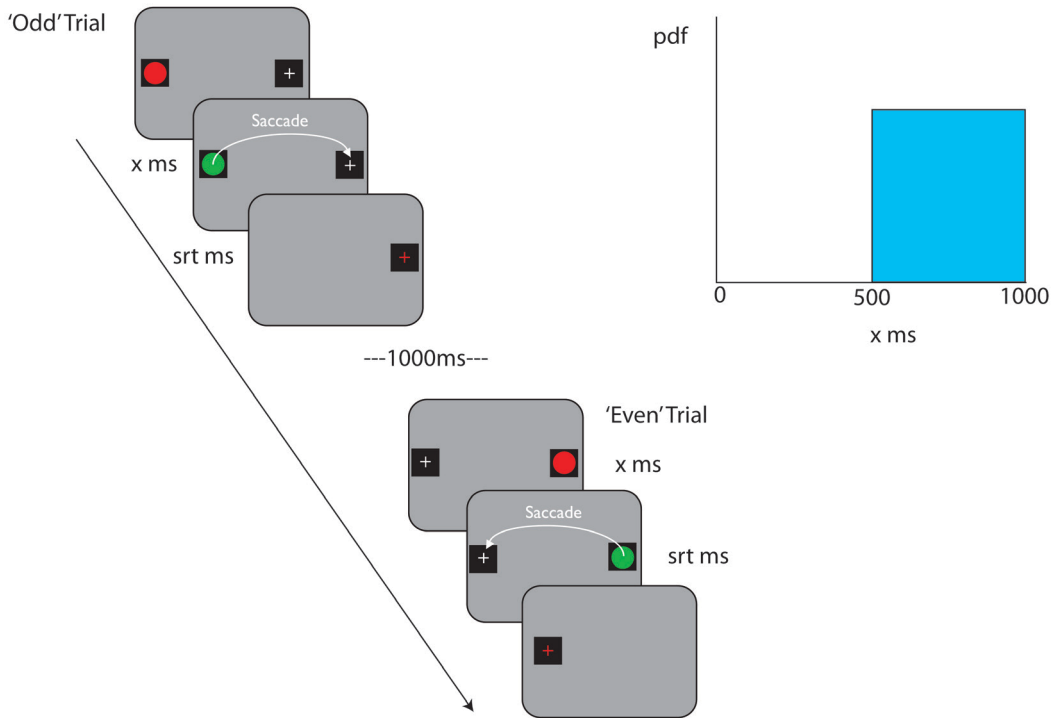



**Figure 2.2 The Saccadic Reaction Time (SRT) Task**

Subjects were asked to attend a red light, which turned green after a variable period of x ms (500-1000ms, mean 750ms, rectangular distribution. They then made a saccade to a target cross on the opposite side of the screen (20 degrees lateral deviation) as quickly as possible. Upon arrival, the target-cross turned red to confirm the completed saccade before a new red traffic light was shown at the new location. Trials therefore alternated left to right, right to left. Subjects completed 100 trials. Saccades made erroneously, before the green light, were excluded from the analysis.

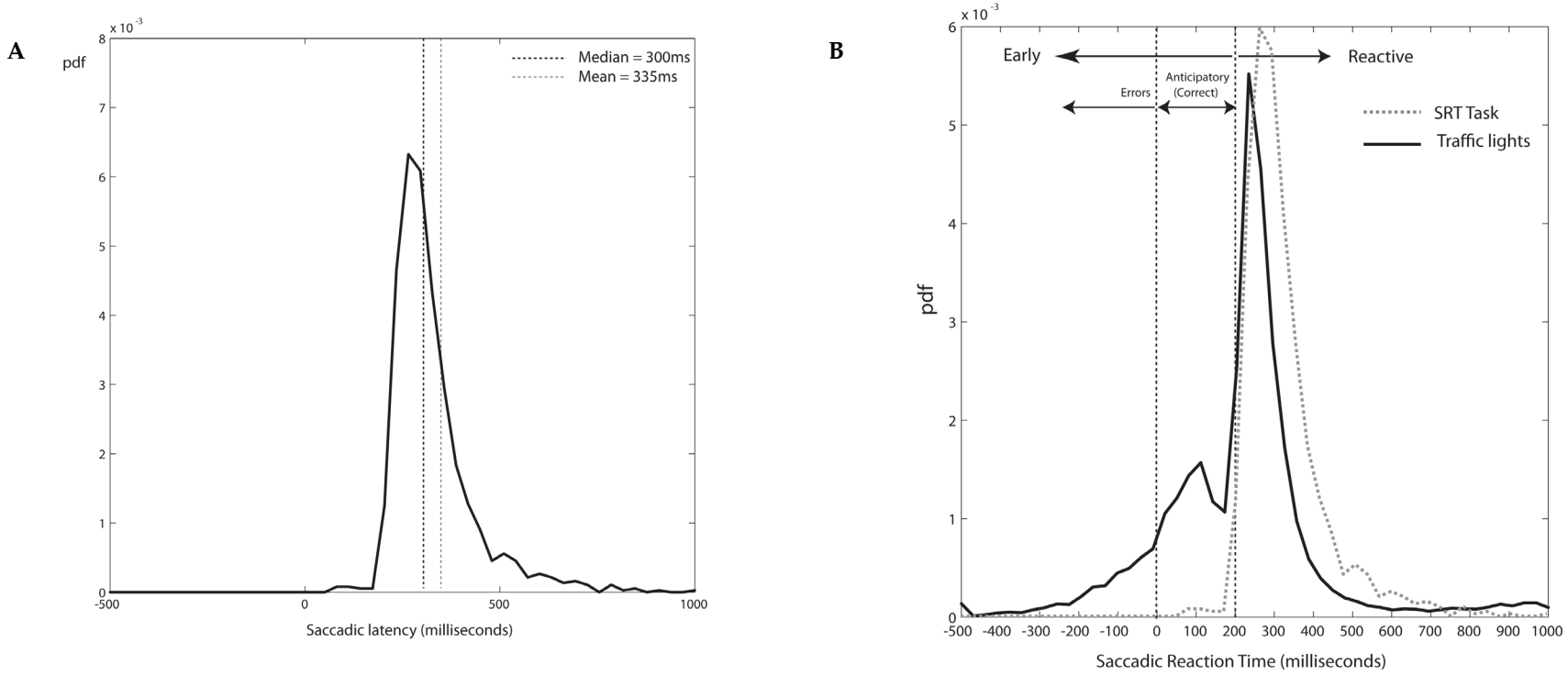



**Figure 2.3 Saccadic Reaction Time task and Traffic Light Task Results for Young Subjects**

**A Saccadic reaction time (SRT) task response distribution (probability density function, pdf) for young controls.**

Participants showed a typical, positively skewed, "recinormal" distribution of saccadic latencies.

**B Traffic Light Task response distributions for young controls.**

A bimodal distribution was apparent consisting of a population 'early' (anticipatory) saccades and 'late' (reactive) saccades. The latter were of similar latency to those seen in the SRT task.

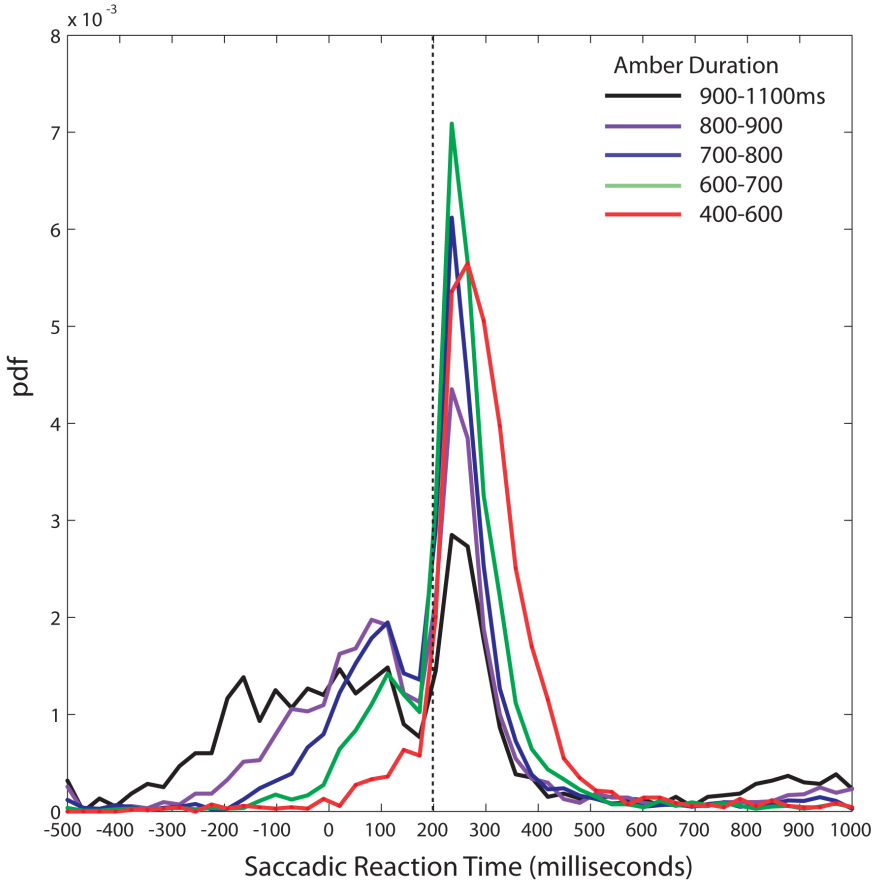



**Figure 2.4 Saccadic response distributions varied with amber duration.**

Displaying the probability density function (pdf) according to the amber duration in each trial reveals two important features of the task response. First, the longer the amber duration, the more likely an early, anticipatory saccade will be generated. Second, the latency of the reactive distribution appears constant for all amber durations.

Zero refers to green light onset.

### 2.3.2 A linear rise-to-threshold model predicts likelihood of saccades arising from reactive and anticipatory distributions

The positively skewed, 'recinormal' distribution of saccades in various, simple, reactive tasks has been well modelled by Carpenter's LATER (Linear Approach to Threshold with Ergodic Rate) model (Carpenter and Williams, 1995). Moreover, in tasks in which the saccade target might be anticipated – as here, but also in gap paradigms where the fixation point is extinguished prior to target onset – the distributions have been modelled well by two LATER units competing in a 'two horse race' (Story and Carpenter, 2009).

Such models assume that a decision threshold must be reached to initiate a saccade (Figure 2.5). Reaching that threshold depends upon the accumulation of evidence in favour of making the decision. In the traffic lights task, as time passes following amber onset, there is increasing expectation of the green light. This form of evidence is accrued slowly. Once the green light comes on, however, there is 100% evidence of the requirement for a saccade, and the GO signal therefore would be expected to lead to rapid accumulation of evidence in favour of generating a saccade.

To model the data from the traffic light task, we assumed two processes, one triggered by the amber light and the other by the green light. A rapid, rise-to-threshold, process that is evoked by the appearance of the green light would describe the distribution of reactive saccades. We further hypothesised that *anticipatory saccades*, driven by an increasing expectation of the GO signal, would be described by a separate, slower and independent rise-to-threshold triggered by the *amber* light onset. Thus we have two rise-to-threshold processes competing to reach decision threshold: an early (anticipatory), slow one evoked by amber onset and a later (reactive), fast one triggered by green onset. According to this model, a saccade is generated by whichever process is first to reach threshold (Figures 2.5 & 2.6).

The likelihood of the first, slow-rising anticipatory process reaching the threshold increases as amber duration lengthens. For very short amber durations, therefore, there is not sufficient time for an anticipatory saccade to be generated, and the green light triggers a rapidly rising reactive process, which reaches threshold first. Nearly all the saccades, for short amber durations, would therefore arise from the reactive distribution. By contrast, in trials with the long amber durations many anticipatory saccades occur because there is sufficient time for the anticipatory process to reach threshold before the reactive process is triggered. There is a 'two-horse-race' between the anticipatory process, which starts earlier but rises to threshold slowly and a later starting but more rapidly rising reactive process.

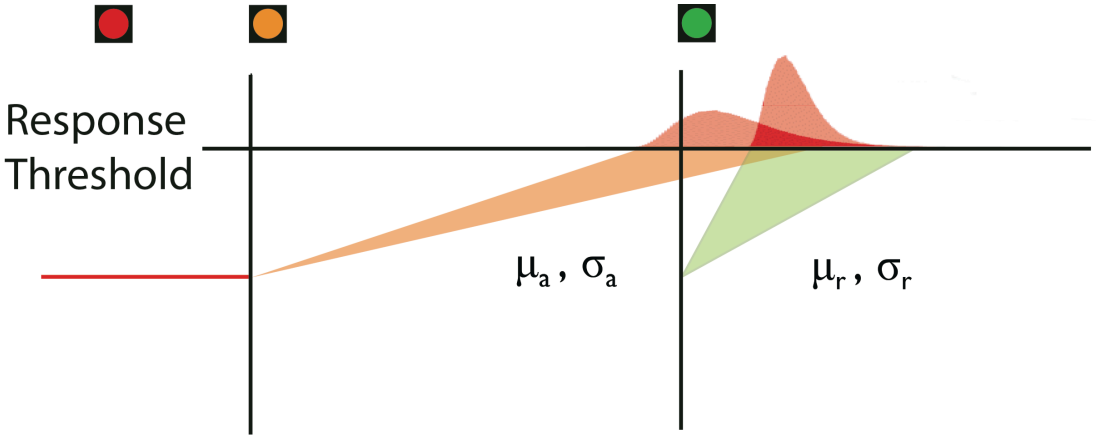



**Figure 2.5 How two LATER Units might describe the observed data.**

It is assumed that a certain "decision threshold" must be reached to initiate a saccade. This threshold may be reached through two forms of 'evidence'. As time passes following the amber onset, there is increasing expectation of the green light. This form of evidence is accrued slowly and produces anticipatory saccades of mean onset $\mu_a$. Once the green light is lit, there is 100% evidence of the requirement for a saccade, so a faster decision process is initiated, producing reactive saccades of mean onset $\mu_r$. Depending upon the amber duration and prior knowledge of the amber duration distribution, one process will win the race on any given trial. As these are biological systems, there is also noise (variability) in the rate of rise of each process. This gives rise to variance in each distribution, $\sigma_a$ & $\sigma_r$.

Formally, the probability that a saccade has occurred by time *t* following amber onset (i.e. the cumulative probability distribution) is given by:

$$\Pr(T \le t) = \Phi_A^{-1}(t) + \Phi_R^{-1}(t - t_0) - \Phi_A^{-1}(t)\Phi_R^{-1}(t - t_0)$$

Where $\Phi_A^{-1}$ and $\Phi_R^{-1}$ indicate cumulative inverse Gaussian distributions describing anticipatory and reactive processes, respectively.

### 2.3.3 Anticipations, Rewards and Errors

We used maximum likelihood estimation (Myung, 2003) to obtain best-fitting mean and variance parameters for each distribution (Figure 2.6D). The model therefore used four parameters: the gradient and variance of the rise-to-threshold process triggered by the amber onset and similarly the gradient and variance of the process triggered by the GO signal. Maximum likelihood parameter estimates were obtained by Nelder-Mead simplex method (*fminsearch* in MATLAB).

Population data for all saccades are shown in the left panels of Figure 2.7, while the corresponding distributions produced by the model are shown on the right. The data are further decomposed into distributions for different amber durations in Figure 2.8, with real data again on the left and model performance using four parameters shown to the right.

Note that if the distributions are plotted with respect to amber onset, one might get the impression there was only one distribution. However, plotting all the data with respect to green onset or decomposing the results as a function of amber duration (even when plotted with respect to amber onset) reveals the bimodal distribution.

In the case of the young subject group, the model estimated a mean for the reactive distribution of 289ms (SD 32ms; median = 289 ms) *from green onset*. We decided to use a cut-off of less than 200 ms SRT to classify saccades as being from the anticipatory distribution (Figure 2.9). This value corresponds to 2.5 SDs from the reactive distribution mean. When modelled individually, 200ms was a minimum of two standard deviations below the modelled reactive mean for each control subject. The group mean for the anticipatory distribution, now computed *from amber onset*, was 1344ms (SD 52ms; median = 1157ms).

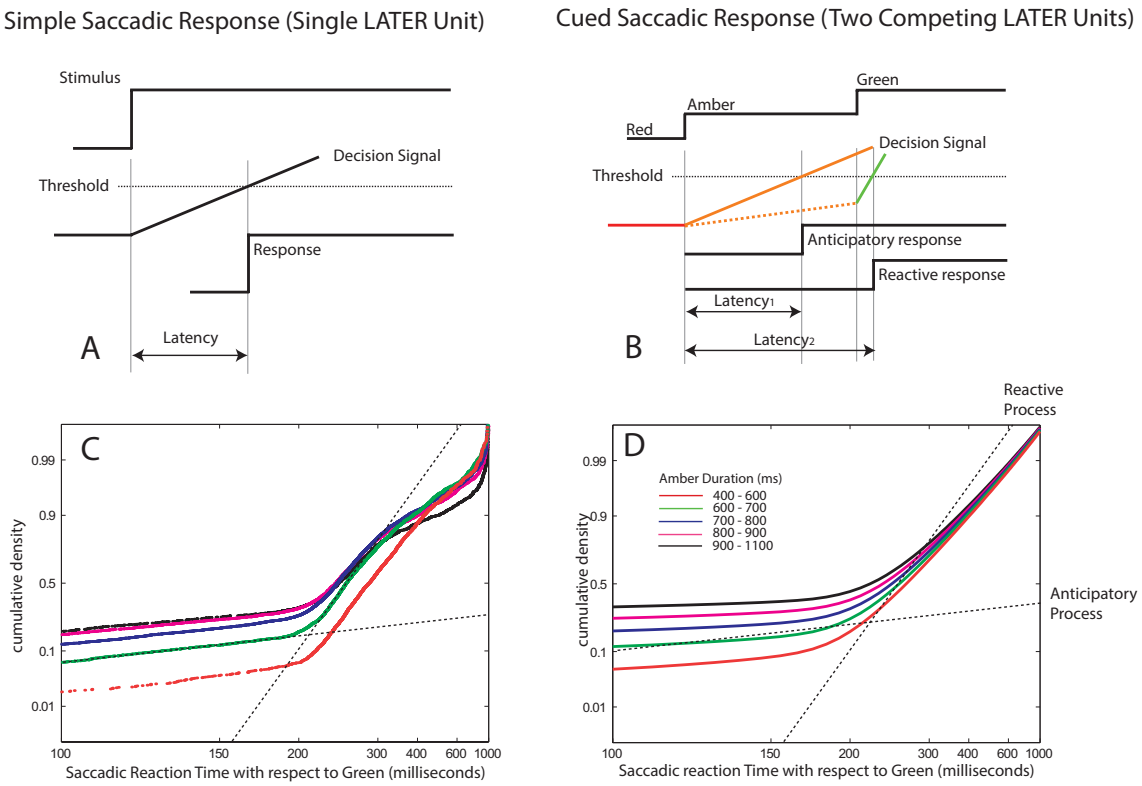



**Figure 2.6 Young volunteer data modelled as two linear rise-to-threshold processes.**

**(A)** Linear rise-to-threshold models predict simple saccadic response distributions. **(B)** We used a model which incorporates two LATER units to estimate means and variances for both reactive and anticipatory response distributions. In this case, saccadic latency depends upon the slope of each linear rising process (and the variability of the slope of each process from trial to trial). For short amber durations, the reactive process, which is steep, will usually reach threshold first (denoted by green line). For longer amber durations, however, the anticipatory process (amber line) triggered by amber onset may reach threshold before the reactive process does. In this example an error occurred because the amber-triggered process reached threshold before green onset. **(C)** Plotting responses on reciprobit axes demonstrates the existence of the two linear rise-to-threshold processes, one starting at amber onset (anticipatory), the other in response to green onset (reactive). **(D)** The gradients and variabilities of these processes were estimated using maximum likelihood estimation and used to parameterize two separate LATER units to model the distributions.

Using the 200ms cut-off, a total of 30.2% of young volunteers' saccades were computed using this model to be from the anticipatory process. Just over two-thirds of these saccades occurred between green onset and 200ms following it, comprising 21.1% (SD 11.1) of all saccades. Thus these saccades were highly rewarded. Overall reward correlated highly with the percentage of anticipatory responses ($R^2$=0.419, $p<0.05$). A weaker but still strongly significant negative correlation between overall mean reaction time and reward was also found ($R^2$= - 0.296, $p<0.05$). Percentage errors were not significantly correlated with overall reward ($R^2$=0.041, p=0.184) but recall that errors were all penalised by a small, flat loss of 10p, regardless of how early they were made with respect to the GO signal onset. Overall, young volunteers made on average 17p per trial (min 7p, max 28p, SD 45).

### 2.3.5 Saccadic distributions in older controls

In contrast to the younger test subjects, older participants did not produce very many anticipatory responses (Figure 2.10). The saccade response distribution for this group did not show a bimodal distribution when plotted with respect to green onset. Of course, not all individuals anticipate equally, but the lack of an early distribution was consistently uniform (Figure 2.11). Instead the shape of the overall distribution for older subjects was very similar to the reactive part of the younger subject distribution. Indeed, if we consider only responses of young controls made after 200ms (the 'reactive' distribution), then the mean RT (319 ms, SD 73 ms) was almost identical to the older volunteers (mean 320ms, SD 80ms).

Due to the lack of an anticipatory saccade distribution in older participants, overall they earned less reward on the task. They made considerably less reward per trial than the young group, with a mean of 10p per trial (min 4p, max 20p, SD 4.1). The correlation between the number of anticipations and reward was not significant ($R^2$=0.191, $p>0.05$), unlike in younger participants. However, reward correlated well inversely with mean latency ($R^2$= - 0.499, $p<0.05$). Similarly to the younger group, errors did not correlate significantly with reward ($R^2$=0.002, $p>0.05$).

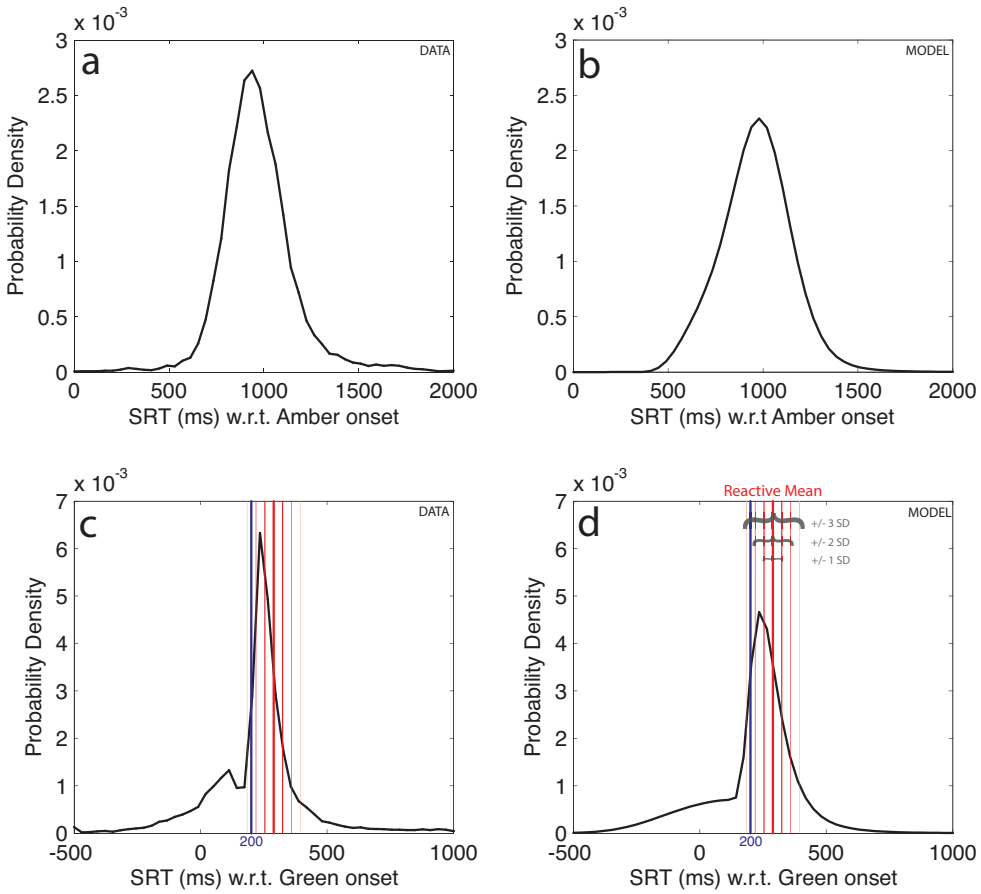



**Figure 2.7 Saccadic response distributions and model distributions.**

Raw data (left panels) and modelled probability distributions (right panels) derived from four parameters (gradient and variance for two rise-to-threshold processes) estimated by maximum likelihood estimation. Plotted with respect to amber onset (a & b), there is a single homogeneous distribution of saccades. However, plotted with respect to the green light onset, the true bimodal distribution is revealed (c & d).

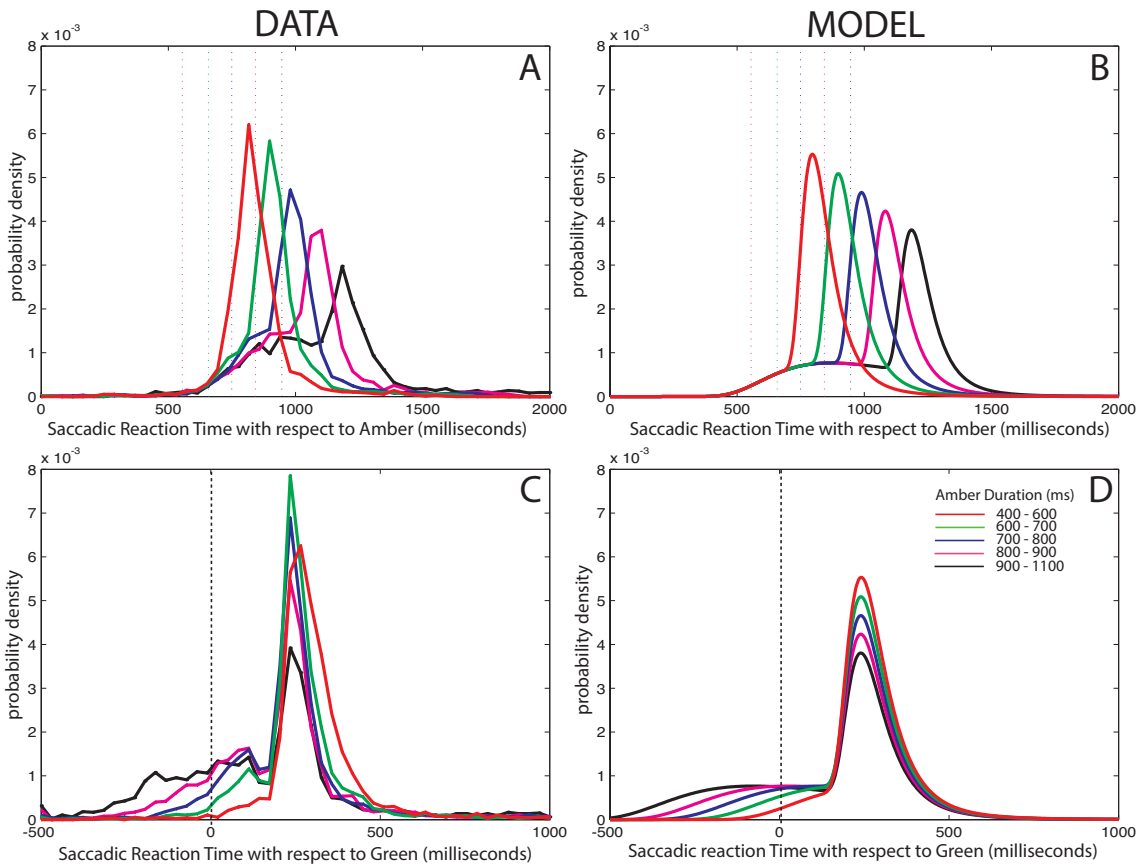



**Figure 2.8 Saccade distributions as a function of amber duration: data and model findings.**

Using maximum likelihood estimation to estimate means and standard deviations for two recinormal distributions, the data (A & C) is well modelled (B & D). Note how the anticipatory component increases with amber duration.

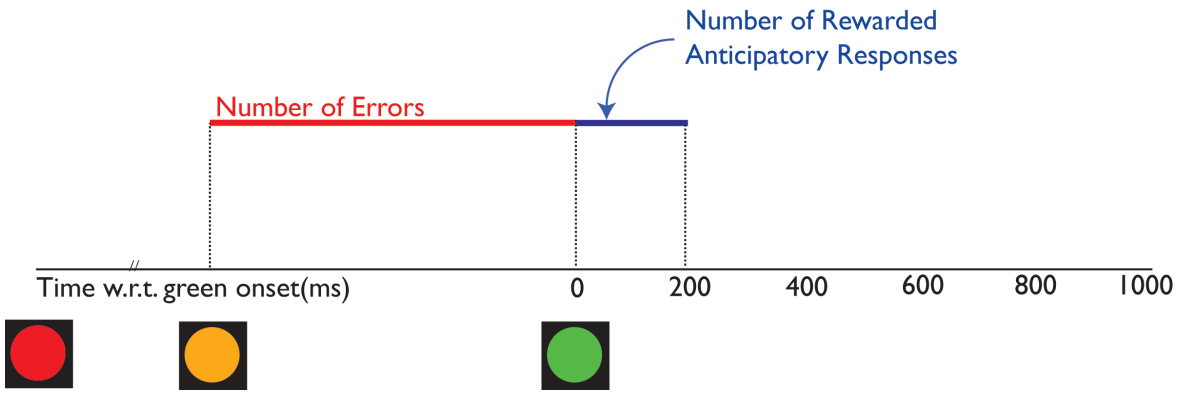



**Figure 2.9 Traffic Light Task Early Responses**

Early responses in the traffic light task occur between the amber light onset and 200ms following the green light. These can be subdivided into errors (early responses occurring in advance of the 'go' signal) and highly rewarded anticipatory responses.

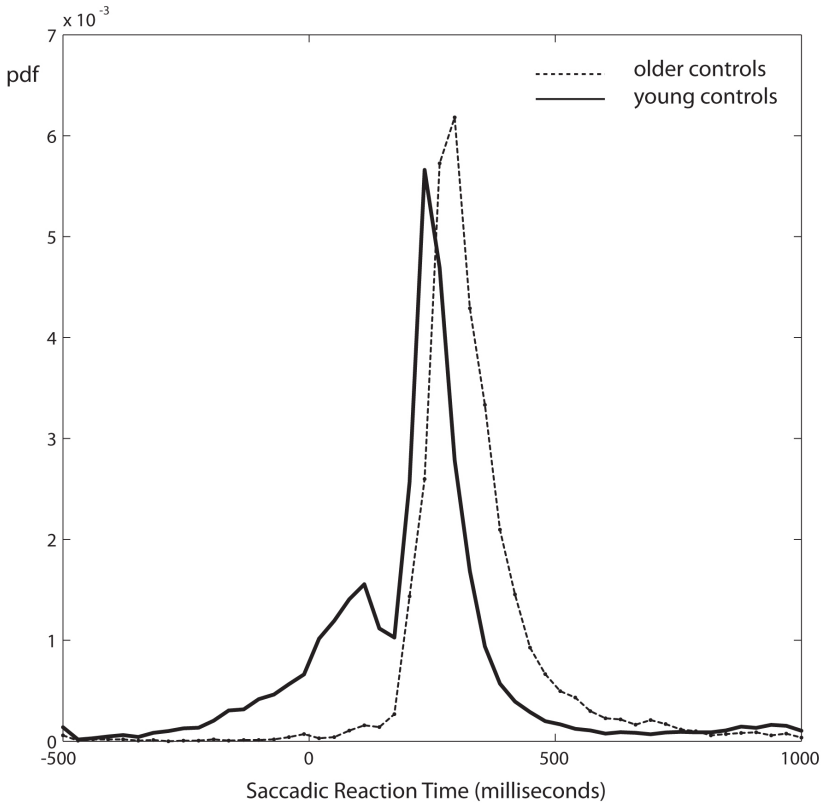



**Figure 2.10 Traffic Light Task saccadic distributions in older volunteers**

Older controls (dashed line) showed little or no anticipation despite similar reactive distribution latency to young controls. The distribution more closely resembles that generated by young controls in the SRT task. The solid line shows data for young controls on the traffic lights task.

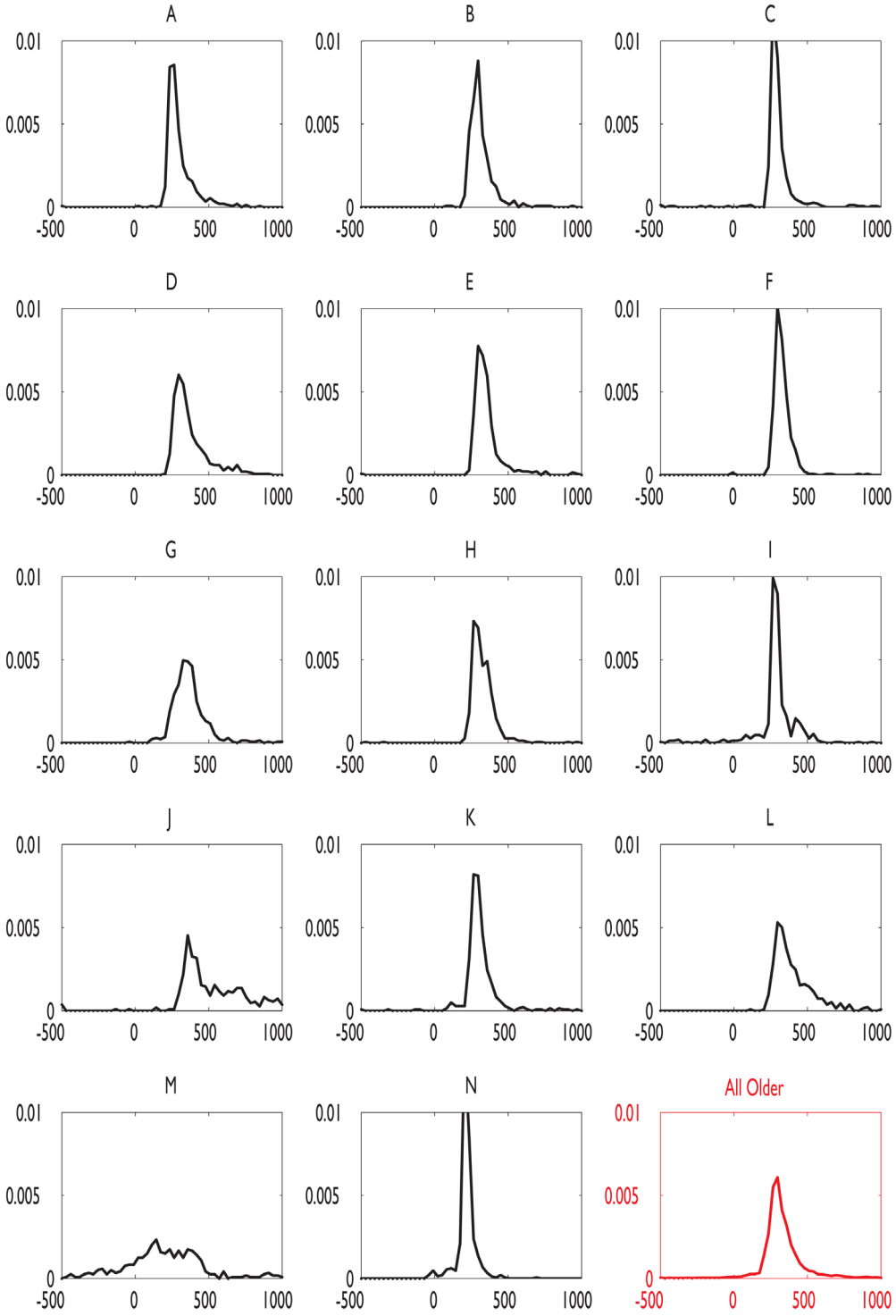



**Figure 2.11 Older Healthy Volunteers: Traffic Light Task**

14 Older healthy Volunteers (Subjects A:N) and the group as a whole. X axes: Response latency (milliseconds), Y axes: Probability Density (no units).

## 2.4 Discussion

We developed a simple saccadic task that can measure decision-making when participants are required to make rapid choices (stay or go) under risk. The task generated two groups of responses in young, healthy volunteers: a reactive distribution and an anticipatory distribution. Separately parameterised linear rise-to-decision threshold processes can model the two distributions. The earlier process is triggered by the amber light and rises slowly to decision threshold whereupon a saccade is triggered. In trials with shorter amber durations, the green light onset (GO signal) triggers the fast rising reactive process that reaches threshold before the anticipatory process can trigger a saccade (Figure 2.5). By contrast, trials of longer amber duration allow the anticipatory process to rise to threshold and generate a saccade before the green light onset. There are therefore increasing numbers of anticipatory responses with increasing amber durations (Figure 2.8).

Task performance, measured as reward obtained, correlated strongly with the percentage of anticipatory, correct responses (i.e., those which fall in the range 0-200 ms after the GO signal). These are programmed before the onset of the green light because it takes ~200 ms to execute a saccade (White et al., 1962). Thus participants had to take a decision about whether to stay and wait longer, or make a response before the green light, risking the possibility of a small penalty against a potentially large reward. Young adults, therefore, made what might be called functionally useful anticipations. They were willing to take a risk and make early responses because overall this would optimize overall reward. However, in older subjects, we found little evidence of anticipatory behaviour. Instead, the vast majority of their responses were triggered after the GO signal and, for them, reward simply correlated inversely with reaction time.

Elderly participants seemed to adopt a more cautious approach on this task, deciding not to make very many risky decisions, perhaps because they were less motivated by the potential rewards and/or more sensitive to the penalty of going too early.

In later life, dopaminergic modulation declines markedly (Li et al., 2010). Imaging of the striatal dopamine transporter (DAT) has been used to demonstrate clear age-related losses of striatal DAT binding from early to late adulthood (Erixon-Lindroth et al., 2005). More specifically, there is a faster rate of D2-like receptor loss in the frontal cortex (11–14% per decade) compared to regions in the temporal cortex (9–12%) and the thalamus (5–6%) (Kaasinen et al., 2000, 2002). This senescent decline has been linked to deficits in processing speed, processing robustness, episodic memory, working memory, cognitive control/executive function and fluid intelligence (Volkow et al., 2000; Erixon-Lindroth et al., 2005; Bäckman et al., 2006, 2010).

An event-related fMRI study comparing pro- and anti-saccades found an age-related shift in activity from posterior to frontal brain regions after young adulthood (Raemaekers et al., 2006). Older adults demonstrated an overall reduction in the blood oxygenation level dependent (BOLD) signal in the visual and oculomotor system. In this study, age did not affect saccade inhibition activity but middle aged and older adults demonstrated increased frontal activation to maintain performance even during simple pro-saccades. Furthermore, connections between

the ventral striatum and dorsolateral prefrontal cortex (DLPFC) seem to differ with age in fMRI BOLD activity during both task learning and in their reward response, with a reduced ventral striatal BOLD response to reward in older subjects (Mell et al., 2009). There is evidence, therefore, that older subjects recruit frontal areas more strongly in order to maintain oculomotor performance and yet they are less sensitive to task rewards, at the striatal level. This deterioration in striatal dopaminergic activity might underlie a decline in goal-directed oculomotor control in older people (Harsay et al., 2010). These and other changes in the brain with aging are also known to alter patterns of non-oculomotor decision-making (Brown and Ridderinkhof, 2009), perhaps related to differential sensitivity to rewards versus losses (Samanez-Larkin et al., 2007). Our paradigm appears to be sensitive to detect such changes, consistent with such a view.

The task might also be useful in studying decision-making in clinical populations, particularly those who appear to be susceptible to making impulsive choices. Pathological impulsivity has been characterized as *rapid* decision-making under risk (Moeller et al., 2001). On this paradigm, one might expect many erroneous, early responses would be characteristic of such behaviour. Of course, there are many existing measures used to index impulsive decision-making (see Chapter 3) (Aragues et al., 2011; Schonberg et al., 2011) but few, if any, examine risky choices under tight time constraints.

Paradigms such as the STOP signal task have been employed to assess how rapidly participants can cancel an on-going motor plan, and patients with impulsive behaviour are impaired on such tasks (Lipszyc and Schachar, 2010). But although the STOP task measures the ability to exert inhibitory control it does not involve a choice to take a risky decision, unlike the traffic lights paradigm.

One important aspect of this new paradigm is that performance can be modelled using an existing framework that has been used to understand the control of saccadic eye movements: linear rise-to-decision threshold (Carpenter and Williams, 1995). Neurophysiological recordings from monkey frontal cortex have demonstrated that activity within neurons steadily increases to prior to saccade initiation and the rate of rise such activity corresponds well to reaction time (Hanes and Schall, 1996; Schall et al., 2002). Thus such models have physiological tractability. A similar conceptual framework has also been used to model performance on the STOP task, but this time with a race between excitatory activity triggered by the early GO cue and inhibitory or braking activity evoked by the later STOP signal (Verbruggen and Logan, 2008).

Such a 'two horse' race also serves the basis for our modelling, but with activity, or accumulation of evidence, rising-to-decision threshold evoked by amber or green light onset both leading to the same result: execution of a response. Story and Carpenter have also used dual LATER units to predict saccadic reaction times in various oculomotor tasks, but their focus was on modelling expectation from fixation offset and response following target onset (Story and Carpenter, 2009). The traffic lights task puts participants in a very different context where they have to decide whether to take a risk to initiate a response in the absence of a GO signal. Embedded within an existing behavioural and physiological framework, it has the potential to

be applied in many different circumstances to assess rapid decision-making under risk in health and disease.

The remaining chapters of this thesis will use this, other oculomotor tasks and other non-motor measures (discussed in Chapter 3) to investigate decision-making differences in patients with focal brain lesions (Chapter 4), healthy volunteers under the influence of dopaminergic drugs (Chapters 5&6), pathological gamblers and patients with Parkinson's disease (Chapter 7).

# 3. Reward Sensitivity, Risk Aversion and Impulsivity

## 3.1 Introduction

Saccadic tasks have been extensively employed to study decision-making in both humans and monkeys (Platt and Glimcher, 1999; Glimcher, 2001; Gold and Shadlen, 2002; Glimcher, 2003; McCoy and Platt, 2005b; Churchland et al., 2008). Studies including direct recording of monkey brain neurophysiology have enabled investigation of the neural substrates of saccadic reward (McCoy et al., 2003; Hikosaka et al., 2006, 2006; Hong and Hikosaka, 2008; So and Stuphorn, 2010). These studies implicate dopaminergic, parietal, reward-sensitive cells (Schultz et al., 1997; Schultz, 2007). Furthermore, pallidal projections to the lateral habenula and subsequent inhibition of dopaminergic neurons in the midbrain are important in modulating saccadic reward learning (Hong and Hikosaka, 2008, 2013; Stephenson-Jones et al., 2013; Tachibana and Hikosaka, 2012).

### 3.1.1 Saccadic measures of reward sensitivity and risk

Reward sensitivity has been demonstrated in human subjects performing oculomotor tasks with reward-induced reduction in saccadic latencies in both pro- and antisaccade tasks (Ross et al., 2011). I adapted a simple saccadic paradigm used in monkeys and shown to induce speeding of saccadic reactions to rewarded targets presented to one side of fixation compared to unrewarded targets on the other side (Hong and Hikosaka, 2008). Such a **lateral reward task**, could prove sensitive to dopaminergic modulation and/or dopaminergic pathology in humans.

The neural substrate of subjective risk preferences has only rarely been investigated (McCoy and Platt, 2005a). Furthermore, the risky element of the oculomotor tasks used has not related to the timing of the eye movement nor has that timing been related to the reward outcome e.g. (Ackermann and Landy, 2013; McCoy and Platt, 2005a; Stritzke and Trommershäuser, 2007; Stritzke et al., 2009). It was therefore necessary to develop another novel paradigm in order to satisfy such requirements.

I designed the **reverse traffic light task** in which subjects must overcome the drive to activate their saccadic motor plan for *as long as possible* to obtain the greatest reward. However, waiting *too long* results in a penalty. Conservative subjects might make earlier responses, despite lower rewards, while impulsive subjects might also be unable to wait. Since there is no exogenous (stimulus driven) saccade initiation, reaction time is irrelevant. The paradigm rather measures subjects' timing and risk aversion. The task is rewarded and therefore reward sensitivity is relevant, but this is also assessed and controlled for with the lateral reward task.

In this chapter, I present results of investigations using these measures in healthy volunteers. The techniques employed here are used in the analysis of data from later chapters of this thesis. In addition, I explore the relationships with established, questionnaire-based measures of impulsivity described below.

### 3.1.2 Non-saccadic measures

#### 3.1.2.1 The Barratt Impulsiveness Scale

An ever-increasing number of personality questionnaires, behavioural measures and other indices of impulsivity exist (Webster and Jackson, 1997). The Barratt Impulsiveness Scale (BIS-11, [see Appendix]) (Patton et al., 1995; Stanford et al., 2009) was chosen here for the assessment of trait impulsivity as it is one of the most widely used impulsivity questionnaires (Congdon and Canli, 2005; Stanford et al., 2009). The scale has been applied in combined behavioural and neuroimaging studies e.g. (Horn et al., 2003) enabling inference about relevant brain areas. Furthermore, for the purposes of these experiments, correlations with oculomotor behaviour have also been demonstrated (Roberts et al., 2011; Aichert et al., 2012). BIS-11 sum scores have shown correlations with behavioural measures of impulsivity such as Go/Nogo commission errors and with oculomotor measures including antisaccade error rates (Aichert et al., 2012).

The 30-item BIS-11 questionnaire measures impulsiveness through items such as "I act on impulse" and "I consider myself always careful". Participants indicate how frequently each statement applies to them on a 4-point Likert scale (*never*, *occasionally*, *often*, and *almost always*). Possible score totals range from 30 to 120, with higher scores indicating greater total levels of impulsiveness. Analysis of the BIS-11 comprises six first order factors: attention, motor impulsiveness, self-control, cognitive complexity, perseverance, and cognitive instability. These first order factors are combined to generate three second order factors: attentional impulsiveness (inability to focus attention or concentrate), motor impulsiveness (acting without thinking), and non-planning impulsiveness (lack of forethought).

#### 3.1.2.2 Cloninger Tri-dimensional Personality Questionnaire

Eysenck proposed a biologically based model of personality that gave rise to related models such as those of Gray, Zuckerman and Cloninger (Acton, 2003). Cloninger (Cloninger, 1986) defines impulsive behaviour as the coexistence of four heritable temperamental traits:

1. High novelty seeking
2. Low harm avoidance
3. Low persistence
4. High reward dependence

The Cloninger Tri-dimensional Personality Questionnaire (TPQ, C R Cloninger 1987 see Appendix) contains 100 true/false items assessing three higher order dimensions of personality including novelty seeking, harm avoidance and reward dependence (see appendix) (Cloninger, 1987). Cloninger suggested that variation in each dimension correlates with activity in a specific mono-aminergic pathway: Novelty seeking was correlated with low basal dopaminergic activity whereas harm avoidance was due to high serotonergic activity and reward dependence was due to low basal noradrenergic activity (Cloninger, 1986).

There is biological support for the dopaminergic theory with respect to novelty seeking: PET scanning with 18F Fallypride (a D2/D3 ligand) in 34 healthy volunteers found inverse

correlation between TPQ novelty seeking scores and D2-like receptor availability in the ventral midbrain (Zald et al., 2008). The theory arises, therefore, that high novelty seekers have accentuated dopaminergic responses to novelty (and other conditions which induce dopamine release) as a result of this low receptor availability. The high novelty-seeking trait correspondingly acts as a good predictor of drug use and other risky behaviours (Howard et al., 1997). The NS scale in particular, therefore, might be a relevant measure for subjects studied in the experiments on dopaminergic modulation in Chapters 5&6.

#### 3.1.2.3 Summary

Investigations described in this chapter using oculomotor tasks are compared with both the Traffic Light Task (Chapter 2) and with established questionnaire measures of impulsivity. Correlations between oculomotor measures and personality indices inform the experiments in the remainder of the thesis.

## 3.2 Methods

All oculomotor task stimuli were programmed in C/C++ and run on a personal computer ((PC), Dell Optiplex 755 running Windows XP SP3). A separate (Dell Precision 380) PC controlled the eye tracker but was networked to the stimulus/display PC. This allowed real-time task feedback responses to eye movements. Eye position and pupil area data were acquired in real time and exported into Matlab R2008a (The Mathworks, Massachusetts, USA) for analysis.

Eye position data was used to detect fixations during each trial. Saccadic latencies were calculated from the onset of the second fixation in each trial (i.e. arrival at target) and referenced to time stamps produced by the onset of the traffic light stimuli. Though blink errors were unavoidably included in the real-time feedback to the participant, blink trials were excluded from our *post hoc* analysis.

### 3.2.1 Saccadic Reaction Time (SRT) Task

This task probed participant's simple saccadic reaction time. This enabled assurance that high reward outcomes on the traffic light task were not merely related to fast reaction times. Moreover, it allowed validation of the putative "reactive" distribution of saccadic responses in the traffic light task.

47 young healthy volunteers (mean age = 20 years; 23 females) and 13 Middle aged controls (mean age 41 years; all male), recruited from the UCL psychology subject pool, completed the SRT task (Chapter 2, Figure 2.2). Subjects were asked to attend a red light that turned green after a period of 500-1000ms. The delay varied randomly (with a rectangular probability distribution) from trial to trial. When the light turned green, subjects make a saccade as fast as possible to a target cross on the other side of the screen. Saccades made before the green light incur an error signal and are not included in the analysis. The next trial starts at the point just reached such that saccades alternate, rightward then leftward.

### 3.2.2 The Lateral Reward Task

The lateral reward task (Figure 3.1) was included in order to assess reward sensitivity. Macaques performing a similar task demonstrated speeding toward targets where they expected a juice reward (Hong and Hikosaka, 2008; Figure 1.5).

21 young healthy volunteers (12 female, mean age 23 years) and 15 middle-aged volunteers (2 female, mean age 40 years) completed the lateral reward task.

Subjects were asked to fixate a central spot for 1000ms before making a saccade to a target appearing 10 degrees to the right or left (50% probability on each trial). The rewarded side changed every 10-14 trials, jittered such that 60 leftward and 60 rightward rewarded sides were encountered by each subject overall, in a 120 trial block. Rewarded trials were acknowledged by the display of a pound coin and a number representing the magnitude of the reward in pence. Reward value was dependent on latency using a similar function to that employed in the Traffic Light Task (Figure 3.2). The reward function was slightly shifted to accommodate longer mean latencies (discovered in piloting) due to the unpredictable target position. A red circle and a zero acknowledged unrewarded trials.

Participants performed two blocks of 120 trials. Their reward for participation was scaled to their total reward accrued across the tasks presented. The difference between the reaction times to the rewarded and unrewarded sides was used as a measure of a subject's sensitivity to reward.

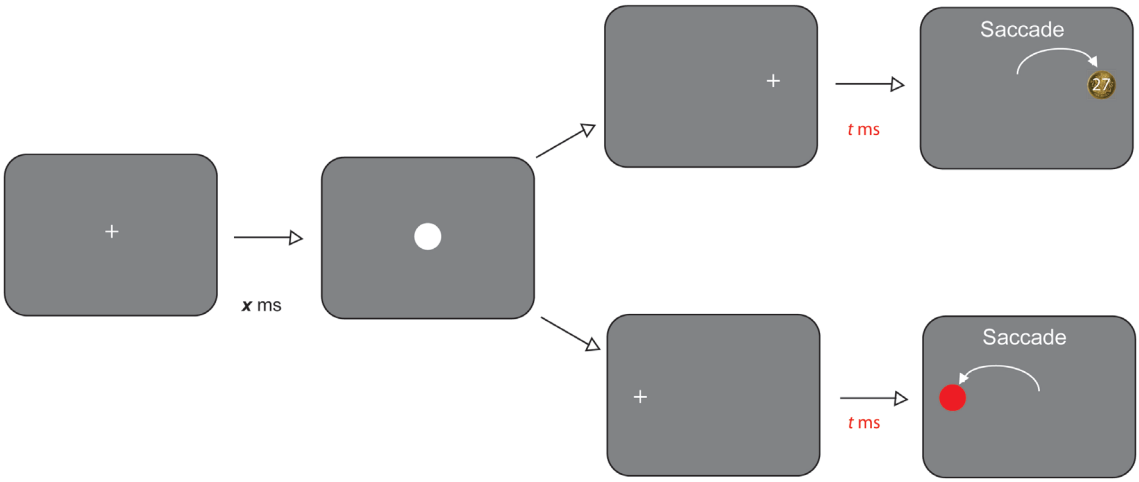
### 3.2.3 The Reverse Traffic Light Task

The reverse traffic light task (Figure 3.3) was introduced to assess participants' willingness to take risk. Responses require a saccade, but the task was designed such that the simple saccadic latency is largely irrelevant. The task reward is dependent upon *when* subjects decide to make an endogenous saccade rather than their ability to react reflexively to an external stimulus. However, their decision to make a saccade is influenced by learning the mean amber duration from previous trials. This requires some early exploratory behaviour and willingness to experience some punished early trials.

The task was administered to 24 young controls (12 female, mean age 23) and 8 middle-aged controls (8 male, mean age 42). In this task, patients were told to fixate a green light that would then turn amber (after 1000ms). They were told to make their saccade at some time during the amber light. It was explained that the later they made their eye movement, the more highly rewarded their response would be. However, were the amber light to turn red before they made their eye movement, they lost 10 pence. The amber light duration was varied randomly from trial to trial selected at random from a Gaussian probability distribution with a mean of 1500ms (SD 500ms). This was intended to force subjects to wait slightly longer on each trial than in the traffic light task and also to avoid "cross-over" effects between tasks, within or across testing sessions.

The closer subjects make their saccade to the red light onset, the greater the reward they received. Due to the changing amber duration, the reward calculation had to be slightly more complex: Reward was derived as an exponentially increasing value related to the red onset on each trial. The reward curve (Figure 3.4) is "fitted" into the variable amber duration on each trial. There is, therefore, not a fixed reward for any particular anticipatory gap, however this contingency ensures that similarly high rewards are achieved for accuracy on each trial.

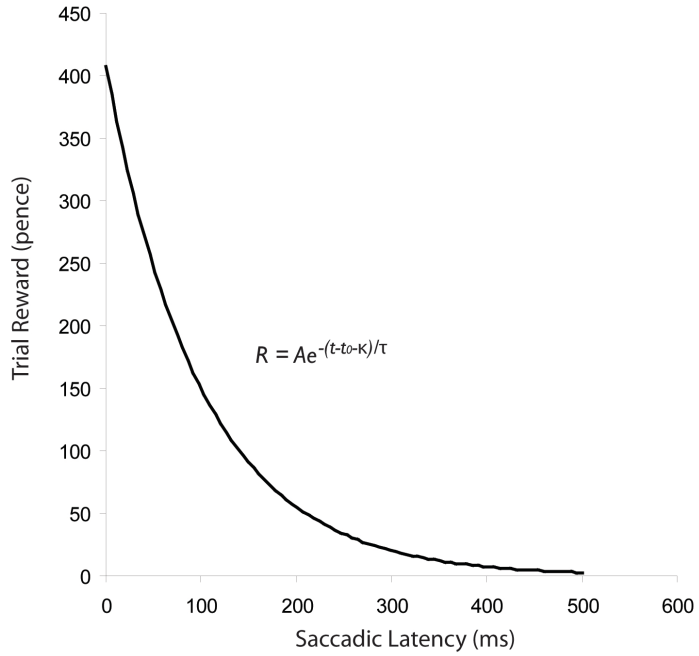
Performance on this task was measured both in terms of reward accrued and in terms of the mean **Stop Anticipatory Interval (SAI)**, the mean amount of time between subjects' saccades and the programmed onset of the red light.




*x = 1000, t = saccadic reaction time*

**Figure 3.1 The Lateral Reward Task**

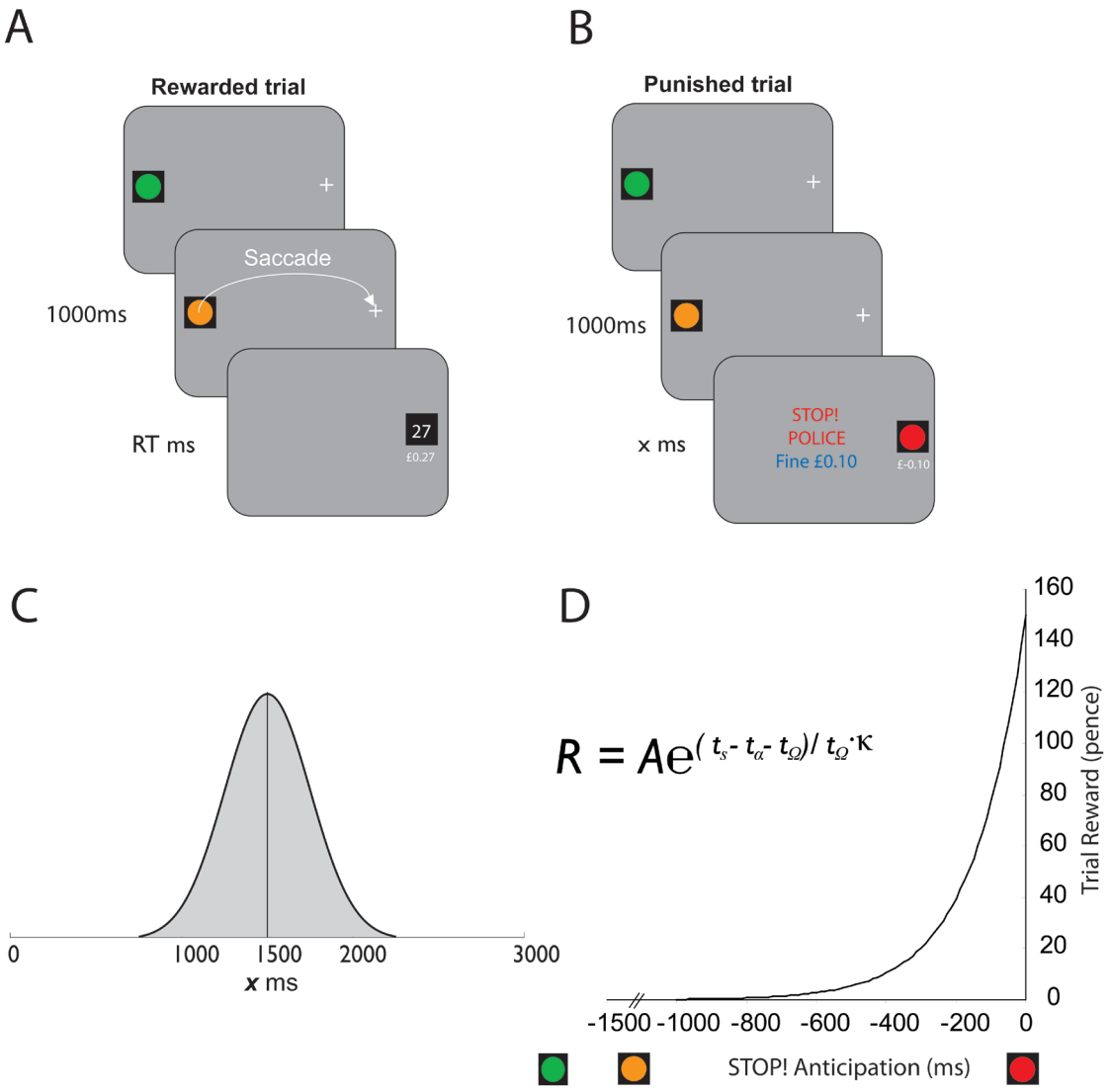
Subjects attend a central fixation spot. After 1000ms of fixation a target appears to the right or left (on average 50% each side, randomly selected). Subjects must make a saccade to the new target and receive a reward dependent upon their reaction time when the target is in the rewarded location. The rewarded location remains fixed for a jittered number of trials such that the side is learned but without the 'switch' (to the other location being rewarded) being anticipated. The unrewarded side yields a score of zero.




*R=reward (pence), A=150, t=saccade onset, $t_0$=target onset, κ = 100, τ=100*

**Figure 3.2 Lateral Reward Task Reward Function**

In the lateral reward task, saccades to rewarded targets received a reward according to the latency of arrival at the target. The reward declines exponentially with increasing latency. The function is similar to that for The Traffic Light Task, but subjects are effectively given a 100ms 'head start' as the unpredictable target position increased mean latencies.




*R=reward (in pence), A=150, $t_s$ = time of saccade, $t_\alpha$ = time of amber onset, $t_\Omega$ = time of red light onset, $\kappa$=0.1*

**Figure 3.3 The Reverse Traffic Light Task**

Participants are asked to fixate a green light, which turns amber (A). The amber duration on each trial varies normally (μ 1500ms, σ 500ms, C). To achieve a high reward, subjects must wait until the amber light is almost finished before making a saccade (A). However, if they wait *too long* the red light onset heralds a fixed penalty of -10p (B). Correct saccades are encouraged by an exponentially increasing reward with reduced STOP anticipation intervals (D).

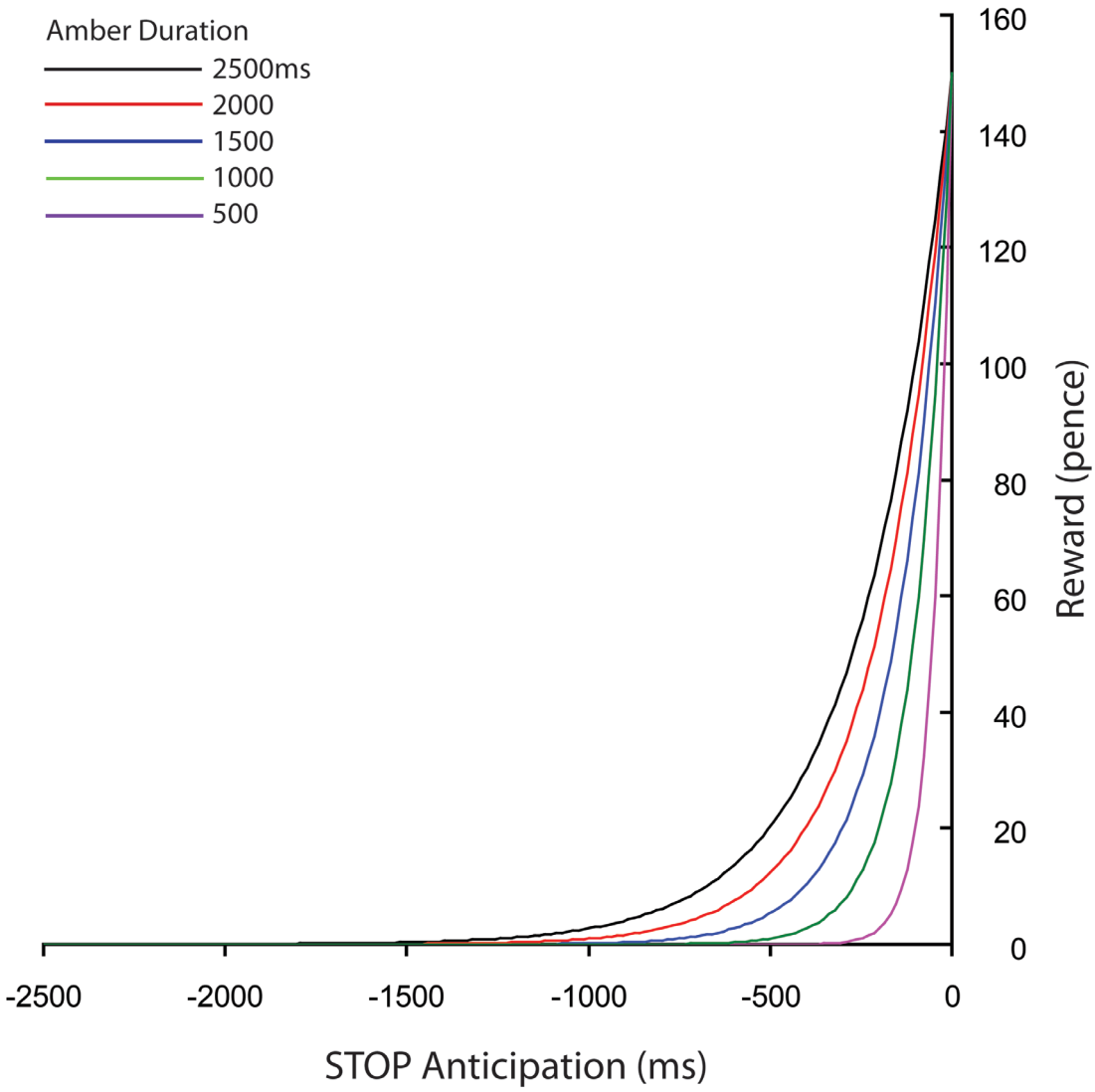



**Figure 3.4 Reverse Traffic Light Reward Function Varies According to Amber Duration**

As the amber duration varies, the exponential reward function is 'fitted into' this interval so that the same maximal reward (150 pence) can be achieved on each trial. That is to say that the calculation of the reward function varies with the amber duration on each trial. For very short amber durations, the reward climbs necessarily more steeply than it does for longer durations.

### 3.2.4 Traffic Light Task

24 young healthy volunteers who had completed the Traffic Light Task (Figure 2.1, see Chapter 2) were invited to take part in the other tasks described in this chapter. In The Traffic Light Task, participants were told that their main aim was to win as much money as possible. They were asked to make rapid eye movements from a 'traffic light' (coloured disc 3 degrees in diameter) to a target cross (3x3 degrees), both presented on a computer monitor (60cm from the chin rest/plane of the eye). The traffic light and target were 10 degrees either side of the screen center (Figure 2.1). Subjects were requested to fixate the traffic light stimulus while it turned from red (duration 1000 ms) through amber to green. They were asked to make their 20 degree saccade to the target cross *as quickly as possible* and as soon after the GO signal as possible. They had a maximum of 1000ms in which to respond.

The reward ($R$) for a successful saccade was calculated by an exponentially decaying discounting function in the form:

$$R = ae^{-\left(\frac{t-t_0}{k_1}\right)}$$

Where $a$ = 150, $k_1$=100 and $t$ represents the saccade onset time relative to green onset ($t_0$, milliseconds).

This steep discounting function (Figure 2.1C) generated disproportionately high rewards for short saccadic reaction times (SRTs). Saccades with latencies of 400ms after green light onset were rewarded with only 2.8 pence; SRT=300ms made 7.5 pence while SRT=200ms generated 20.3 pence. Saccades with shorter latencies than this were far more highly rewarded: a response with SRT=100ms made 55.2 pence and 50ms led to a reward of 91.0 pence. But note that to make these high rewards, subjects would have to anticipate green light onset because saccades typically take ~200 ms to programme (White et al., 1962). In other words, they would have to make a decision – take a risk – to programme a saccade *before* the onset of the GO! signal. Such saccades, with latency <200ms and reward >20 pence were signalled by a reinforcing "Kerching!" sound whereas slower correct responses resulted in a simple "Ping".
Saccades that were actually made before the green light incurred a small, fixed penalty of 10 pence. Error trials were accompanied by an unpleasant audible beep and a visual warning, 'STOP POLICE! Fine £0.10.'.

The timing of the GO signal (green light) onset was not absolutely predictable from trial to trial. Instead, the duration of the amber light was randomly selected on each trial from a normal distribution (mean 750ms, SD 125ms). To perform optimally, participants therefore needed to make as many rewarded anticipations as possible, while keeping errors to a minimum. They had to make a choice of whether to stay (wait longer) or go and risk a small penalty versus the possibility of a large reward.

On gaze arriving at the target cross (fixation tolerance 2°), subjects received both aural and visual feedback on their performance. They were shown the reward (in pence) on the trial just

completed, and a running total beneath (in pounds). There were also aural cues to trial performance. For rewards of less than 20 pence, they heard a 'ping'. For rewards of 20 pence or more, they heard a more rewarding 'kerching!' sound. The target cross was then replaced by a red light (circle) and a target cross now appeared on the opposite side of the screen to begin the next trial. To perform optimally, subjects should therefore make as many anticipations as possible, but as few errors as possible. Subjects performed ten blocks of fifty trials, the first trial in each block started from a left sided stimulus (rightward saccade) and then alternated.

The main performance indicator for subjects was the reward achieved on each trial and the cumulative reward at the end of each block of 50 trials. We have established that the number of anticipations (responses made with latency <200ms) relative to errors (responses made before the green "Go!" signal, <0ms) is a good measure of task performance (Chapter 2).

### 3.2.5 The Barratt Impulsiveness Scale (BIS-11)

Subjects (n=201) were recruited by email from the staff and students of University College London. They were invited by group email to complete an on-line (html) version of the BIS-11 (Patton et al., 1995) [see appendix], which was then submitted electronically. The resultant text string was converted into scores and subscales using a program written in the PERL programming language. Ethical approval was sought from and granted by the UCL graduate research ethics committee. These results of this survey were used as normative data for comparison with studied groups in the experiments described in this and later chapters. All subjects recruited to perform oculomotor tests were also administered the BIS-11 prior to eye movement testing.

### 3.2.6 Cloninger Tridimensional Personality Questionnaire (TPQ)

TPQ (version IV, Cloninger (1987), see Appendix) data was collected from 36 UCL students (17 male, 19 female, mean age 22.9 years (range 18-33 years, SD 3.83)). The questionnaire contains 100 short statements that might describe attitudes, opinions, interests or feelings. Subjects were asked to read each statement carefully and simply marked whether they agreed or disagreed with each statement by marking it true or false. The questionnaire took most subjects 10-15 minutes to complete but they were able to take as long as they liked. Completed questionnaires were scored using Cloninger's scoring keys and analysed using Matlab R2008a (The Mathworks, Massachusetts, USA). The same subjects had also completed the BIS-11 questionnaire.

### 3.2.7 Analysis

Results are reported for each of the new tasks first of all. A cohort of 24 young volunteers was selected to perform all of the tasks and measures for the purposes of seeking correlations. Questionnaire data is discrete, rather than continuous, and therefore Spearman ranking is applied as a non-parametric test of correlation. For continuous data obtained from eye movement tasks, Pearson Correlations are reported.

## 3.3 Results

### 3.3.1 SRT Task

Young volunteers (n=47) performing the SRT task produced typical recinormal distributions (Reddi and Carpenter, 2000) of saccades with mean 338ms, (SD 68ms, median 315ms) (Figure 3.5A, see Chapter 2). The middle-aged volunteers (n=13) produced a similar recinormal distribution (Figure 3.5B). An *F*-Test revealed that the two samples did not differ significantly in variance [p(F<=f) = 0.37]. The older group were slower to react, with a mean SRT of 411ms (SD 56ms, median 394ms). This difference was statistically significant (2-Tailed Student T-test, t(56) = -3.91, p<0.001).

### 3.3.2 Lateral Reward Task

On the lateral reward task, the young group (n=21) unrewarded saccade latency was non-significantly longer (mean 228ms, SD 52ms) than the rewarded latency (mean 221ms, SD 50ms, 1-Tailed Student T test, t(40) = 1.04, p=0.15). Likewise, the middle-aged group (n=15) unrewarded saccade latency was non-significantly longer (mean 235ms, SD 49ms) than the rewarded latency (mean 230ms, SD 49ms, 1-Tailed Student T-test, t(28)=0.74, p=0.23). There were no significant differences in latency between the two groups in either unrewarded or rewarded saccades, but the trend was for the young group to be faster in both conditions.

### 3.3.3 Reverse Traffic Light Task

On the reverse traffic light task, I refer to the difference between the programmed time of the "Stop!" signal (red light) and the time at which subjects made their saccades as the **Stop Anticipation Interval (SAI)**.

*Young Volunteers*

Young volunteers (n=24) anticipated the stop signal with a mean SAI of 370ms (SD 149ms, median 393ms) (Figure 3.6). This led to a mean reward of 12.9 pence (SD 5.1p) per trial (Figure 3.7B). The pseudo-normal distribution of saccade onset with respect to the amber light is shown in Figure 3.7A. The mean onset was at 1131ms (SD 155ms, median 1089ms), so participants responded, on average, earlier than the mean amber duration (1500ms).

*Middle Aged Volunteers*

The middle-aged controls (n=13) produced a SAI that was non-significantly greater at 393ms (SD 89ms, median 402ms) than the younger group. This generated a lower mean reward of 9.3 pence per trial (SD 3.1p, Figure 3.8B). The group performance resulted from a similar distribution of reaction times with respect to the amber light onset; with a mean of 1088ms (SD387ms, median 1072ms) see Figure 3.8A. This is even earlier than the younger group with respect to the mean amber duration.

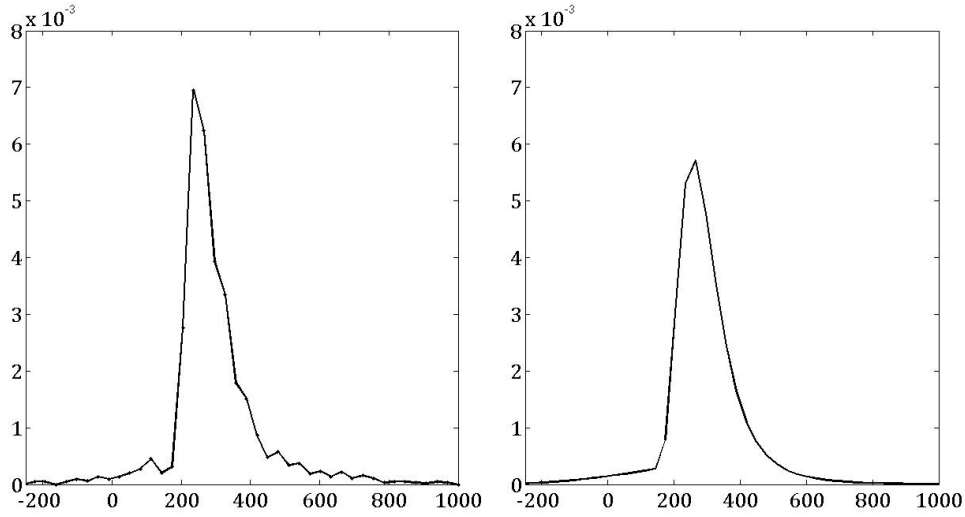



**Figure 3.5A Saccade distribution produced by young volunteers (n=46) performing the SRT task.**

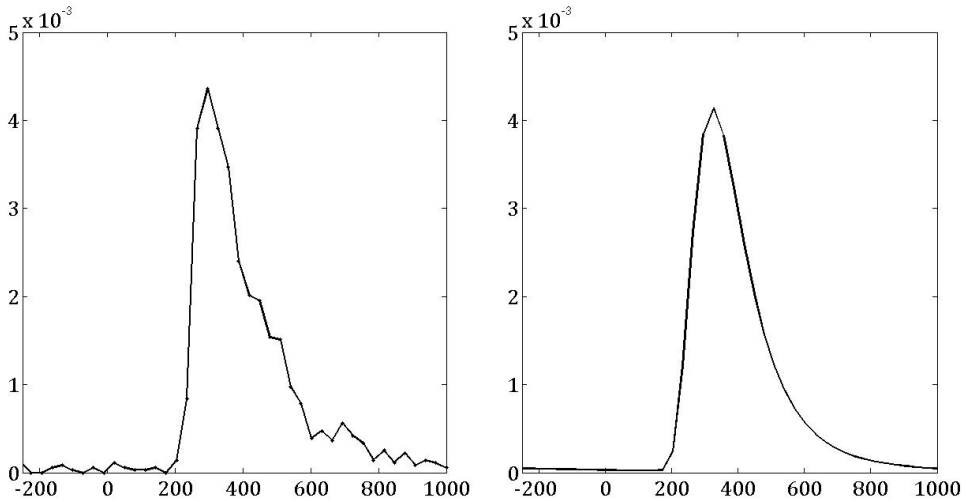



**Figure 3.5B Saccade distribution produced by middle-aged volunteers (n=13) performing the SRT task.**

x axes: saccade onset latency (milliseconds)
y axes: probability density

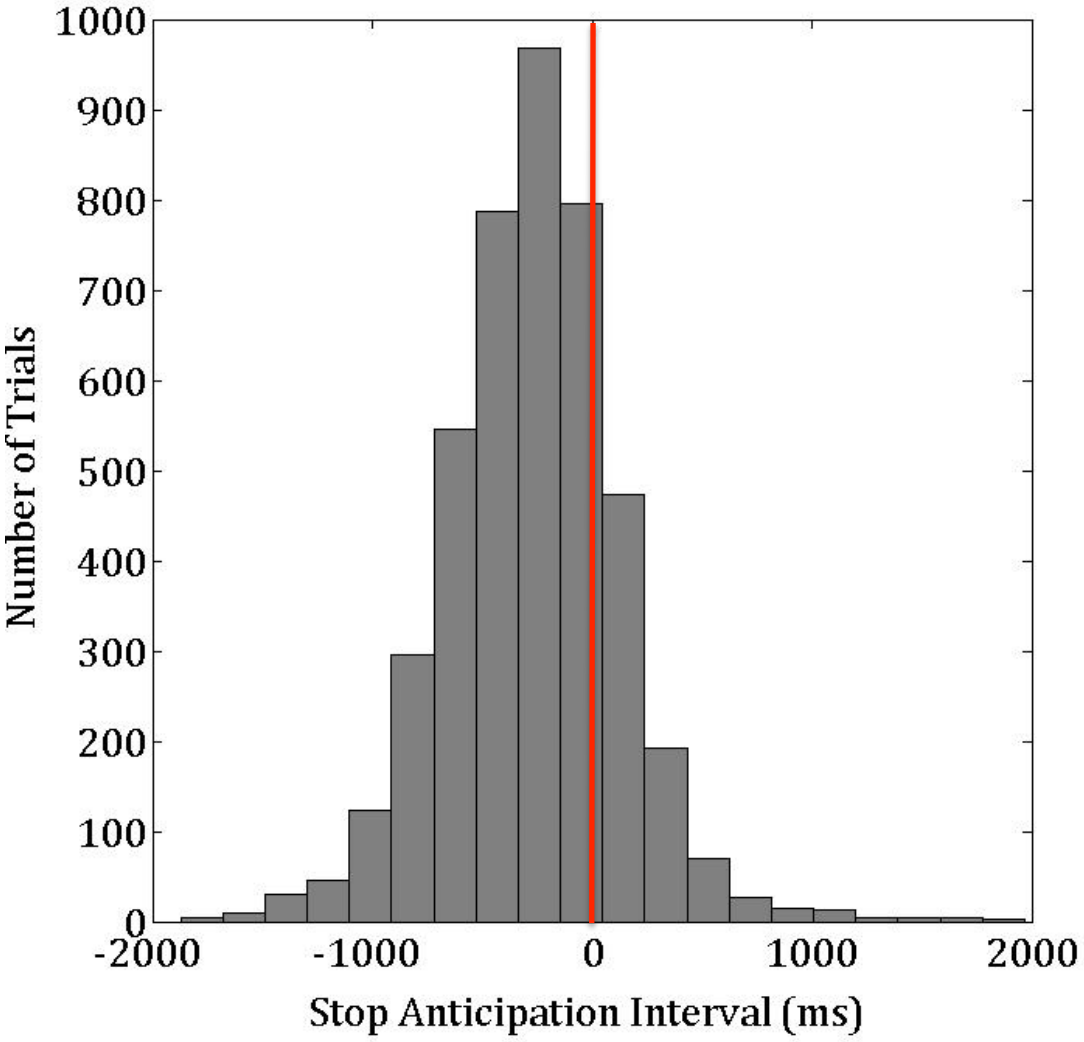



**Figure 3.6 Stop Anticipatory Interval on Reverse Traffic Light task**

The stop anticipatory interval (SAI) is plotted for 24 young volunteers after being multiplied by -1 (in order to visually replicate the task where the stop signal occurs at time = 0). SAI is calculated by subtracting the saccadic response latency (with respect to amber onset) from the stop signal latency (time of red light onset) on each trial.

The red line represents the red light onset.

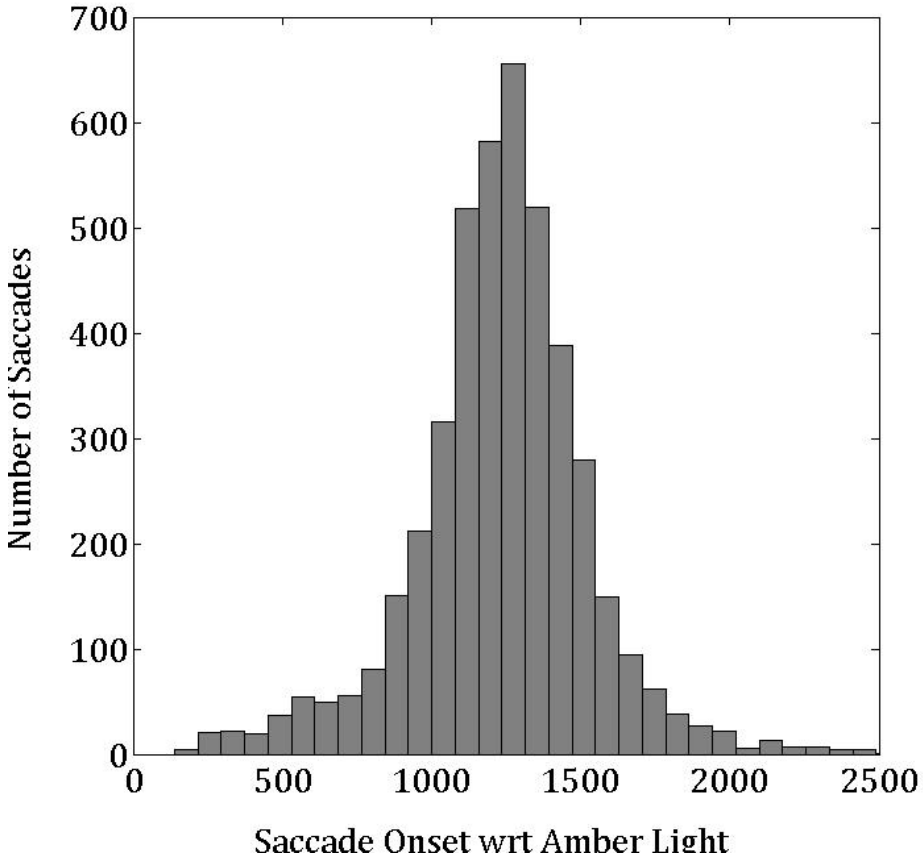



**Figure 3.7A** **Reaction Times from amber onset for young volunteers**

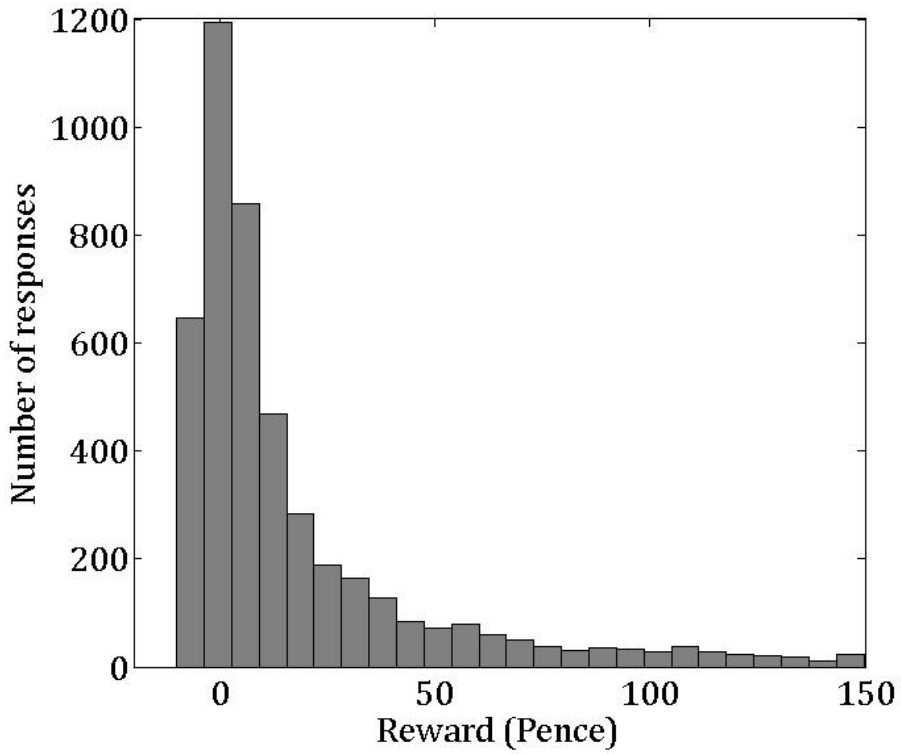



**Figure 3.7B** **Reward Distribution for young volunteers performing the reverse traffic light task**

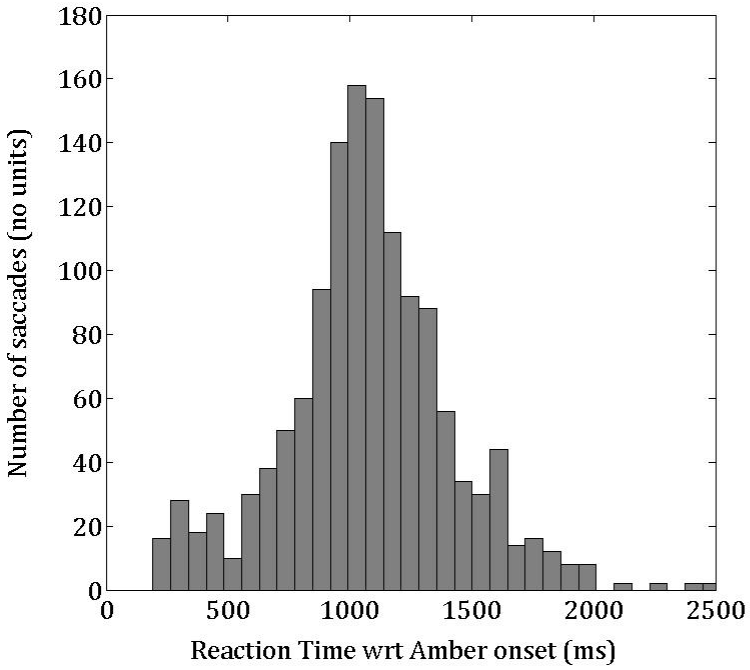



**Figure 3.8A Reaction Times from amber onset for middle aged volunteers performing the reverse traffic light task.**

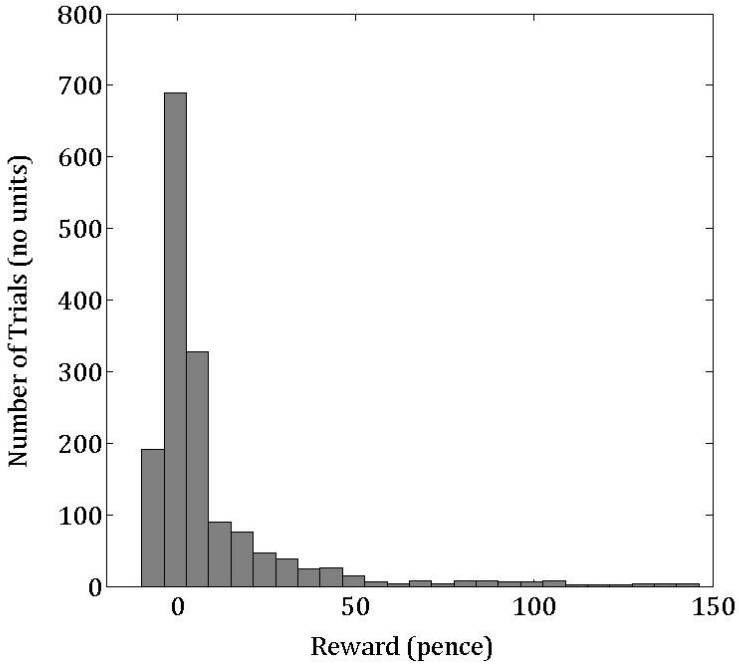



**Figure 3.8B Reward Distribution for middle aged volunteers (n=8) performing the reverse traffic light task.**

### 3.3.4 BIS 11

The UCL data (Figures 3.9 & 3.10) is similar to that reported in the Baylor study (see Table 3.1 and (Patton et al., 1995)). The mean total BIS-11 score was 61.03 (SD 9.17, range 42-92). This was not significantly different (using Welch's T-test (Welch, 1947)) from the Baylor study mean (63.82, SD 10.17). There were no significant gender differences for the total or any of the sub-scores in the UCL group.

There was, however, an effect of age on the UCL BIS-11 data: Subjects indicated their age as 18-25, 26-35, 36-45 or 46-55 (older categories were available but there were no respondents in these categories). The 18-25 year olds (n=111) scored significantly lower than the other age groups combined ($BIS_{(18-25)}$ total mean=59.68, SD 8.52; $BIS_{(rest)}$ mean = 62.69, SD 9.70; 2-Tailed Student's T test: $t(198) = -2.33$, $p=0.02$). This total difference was mostly due to a significant differences in the motor impulsiveness (MI) factor ($MI_{(18-25)}$ mean= 21.3; $MI_{(rest)}$ mean = 23.0; 2-Tailed Student's T test: $t(199) = -3.18$, $p<0.01$).

Despite being very few in number, the oldest group (46-55, n=6) had a significantly lower mean BIS-11 score (BIS total mean=53.00, SD 7.77) than the remainder ($BIS_{(46-55)}$ mean= 53.00; $BIS_{(rest)}$ mean = 61.3; 2-Tailed Student's T test: $t(198) = -2.21$, $p=0.03$). By contrast, the 26-35 year olds (n=65, BIS total mean=63.09, SD 9.07) and 36-45 year olds (n=18, BIS total mean=65.00, SD 10.98) both scored *higher* when compared to the remainder. The 26-35 year old group was large enough for this result to reach statistical significance: $BIS\text{-}11_{(26-35)}$ mean = 63.09; $BIS\text{-}11_{(rest)}$ = 60.1, 2-Tailed Student's T test: $t(198) = 2.18$, $p=0.03$); $BIS\text{-}11_{(36-45)}$ mean = 65.00; $BIS\text{-}11_{(rest)}$ = 60.7; n.s.). These differences may reflect sampling differences and/or natural changes in self-report with age as well as real differences in impulsivity with increasing age.

The young volunteer group who completed all of the measures were also significantly more impulsive as rated on the BIS-11 (mean = 68.83, SD 10.01; 2-tailed Student T-test, $t(223)=3.06$, $p=0.002$).

Significant differences were found in total scores between both the youngest and the oldest groups of subjects when compared with the remaining groups. Both of these groups scored lower on the BIS than the two middle-aged groups, who were rated as more impulsive.

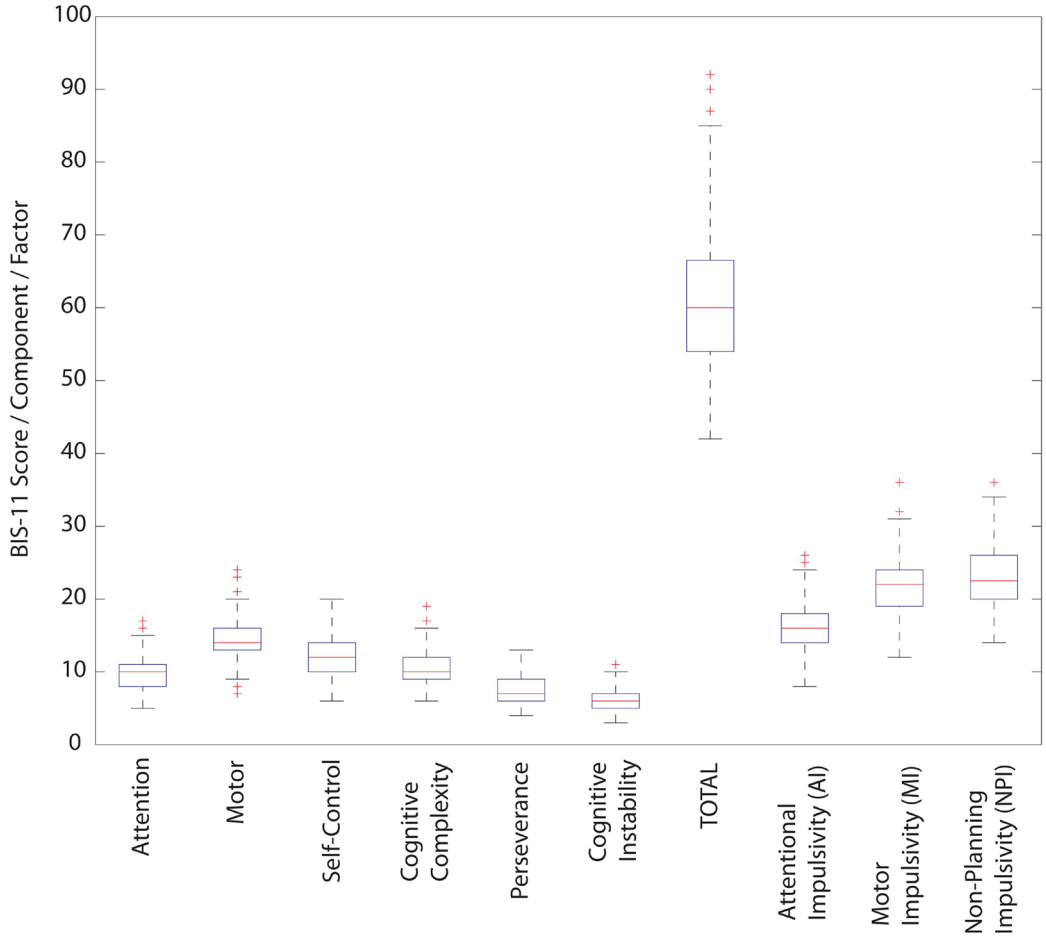



**Figure 3.9** **Box and whisker plot of responses to the BIS-11 from the survey of 201 UCL students and staff.**

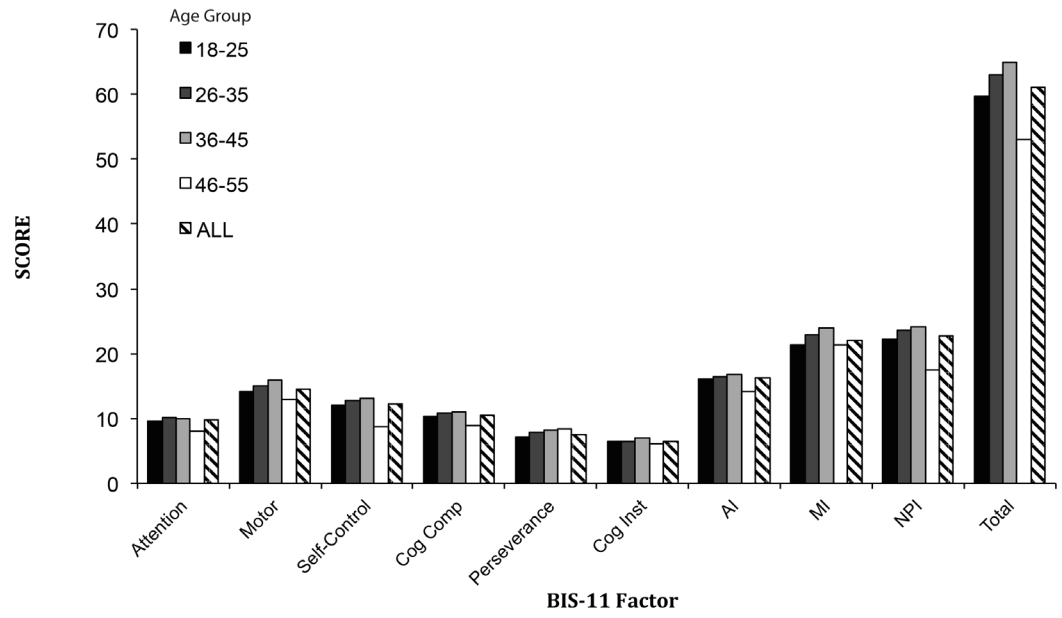



**Figure 3.10** **BIS-11 scores, factors and sub-factors by age group from the UCL survey.**

| *Bis-11 totals* | *Males* | | *Females* | | **Whole Group** | |
|---|---|---|---|---|---|---|
| *Group* | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* |
| **UCL Respondents** (m72, f129) | 61.3 | 8.57 | 60.9 | 9.51 | 61.03 | 9.17 |
| **Young Volunteers (m12, f12)** | 68.83 | 10.01 | 61.15 | 17.82 | 67.13* | 9.67 |
| **Middle Aged Controls** (m11, f3) | 65.82 | 12.60 | 64.33 | 11.02 | 65.50 | 11.88 |

**Table 3.1 BIS-11 Scores**

There were no significant differences between the UCL and middle-aged controls. However, the young volunteers were also rated significantly more impulsive than the UCL group,. *2-tailed Student T-test, t(223)=3.06, p=0.002.

### 3.3.5 Tridimensional Personality Questionnaire (TPQ)

No significant differences were found between male and female scores on the TPQ (Table 3.2). The scores were also similar to previously reported UK data (Otter et al., 1995) see appendix.

### 3.3.6 Between-Measure Correlations

A main aim of the experiments described in this chapter was for comparison and validation of novel and established measures of rewarded decision making and impulsivity. Correlations were sought between performance indicators from each of the oculomotor tasks for 24 healthy young volunteers (12 female; mean age 23) and selected BIS-11 and TPQ scores. Such correlations have previously been demonstrated with psychometric tasks including those studying oculomotor behaviour. I have not reported *within task* or *within measure* correlations here. The statistical significance of each correlation is first tested individually. I later highlight those correlations that withstand Bonferroni correction for multiple comparisons.

There were no BIS-11 correlations with mean SRT task saccadic latencies. However, there were three main points of correlation between the BIS-11 and other oculomotor task performance indicators (Table 3.3).

The indicators selected included:

a) Reward on the **Reverse Traffic Light Task** (RTL); RTL Stop Anticipation Interval (SAI)

b) Errors on the **Traffic Light Task** (a putative marker of dysfunctional impulsivity)

c) Anticipations (correct responses made at <200ms): Errors (incorrect responses made at <0ms) ratio (AER) on the **Traffic Light Task** (a marker of functional impulsivity)

d) Mean saccade latencies to unrewarded (LRU) and rewarded (LRR) targets on the **Lateral Reward Task**.

The results of this analysis found that:

1. There was a significant positive correlation between the Attention (first order factor) score and reward in the reverse traffic light task (Spearman's Rho (22df) = 0.475, p=0.019). This result is consistent with poor attenders (as rated by BIS-11) performing better on this task. This may reflect the lack of external stimulus for a saccade or perhaps an unintended advantage for those subjects who were prone to allowing their minds to wander during the task.
2. The Motor (BIS-11, first order factor) score correlated significantly and positively with reward in the reverse traffic light task (Spearman's Rho (22df) = 0.445, p=0.029). Higher scores in this dimension also negatively correlated with both errors on the Traffic Light Task (Spearman's Rho (22df) = -0.457, p=0.025) and saccadic latencies in the Lateral Reward Task (both unrewarded (Spearman's Rho (22df) = -0.412, p=0.046) and rewarded (Spearman's Rho (22df) = -0.439, p=0.032).
3. The Attentional Impulsiveness Dimension (second order factor) was significantly positively correlated with reward in the Traffic Light Task (Spearman's Rho (22df) = 0.636, p<0.001). This was associated with a negative correlation with Stop Anticipation Interval (SAI), as one would expect (Spearman's Rho (22df) = -0.420, p=0.041). This dimension also positively correlated with a greater Anticipations:Errors Ratio (AER) in The Traffic Light Task (Spearman's Rho (22df) = 0.492, p=0.015). It was also negatively correlated with mean saccade latency to rewarded targets in the Lateral Reward Task (Spearman's Rho (22df) = -0.430, p=0.036).

TPQ scores did not significantly correlate with any oculomotor task indices.

| *TPQ Scores* | *UCL Male N=17* | | *UCL Female N=19* | |
|---|---|---|---|---|
| **Novelty Seeking** | *Mean* | *SD* | *Mean* | *SD* |
| **NSI** | 6.00 | 1.37 | 4.89 | 2.11 |
| **NS2** | 2.88 | 1.87 | 4.05 | 2.20 |
| **NS3** | 4.12 | 1.83 | 3.58 | 1.84 |
| **NS4** | 6.18 | 2.21 | 5.16 | 1.89 |
| **Total NS** | 19.18 | 5.41 | 17.68 | 5.62 |
| **Harm Avoidance** | *Mean* | *SD* | *Mean* | *SD* |
| **HA1** | 2.82 | 2.04 | 3.21 | 2.46 |
| **HA2** | 2.29 | 2.08 | 3.37 | 2.17 |
| **HA3** | 2.24 | 1.75 | 2.68 | 1.95 |
| **HA4** | 3.29 | 2.23 | 3.05 | 3.05 |
| **Total HA** | 10.65 | 6.14 | 12.32 | 6.84 |
| **Reward Dependence** | *Mean* | *SD* | *Mean* | *SD* |
| **RD1** | 3.65 | 1.17 | 3.74 | 0.81 |
| **RD2** | 4.53 | 2.00 | 5.00 | 2.38 |
| **RD3** | 6.94 | 2.77 | 7.42 | 2.83 |
| **RD4** | 2.82 | 1.38 | 2.58 | 1.64 |
| **Total RD** | 17.94 | 4.62 | 18.74 | 4.63 |

## Table 3.2 TPQ scores from UCL Students

There were no significant differences between male and female scores in the UCL data. For comparison with normative data, see appendix.

| *Score* | *Attention* | *Motor* | *Self-Control* | *Cognitive Complexity* | *Perseverance* | *Cognitive Instability* | *AI* | *MI* | *NPI* | *Total* |
|---|---|---|---|---|---|---|---|---|---|---|
| RTL £ | 0.475, p=0.019 | 0.445, p=0.029 | | | | | **0.636, p<0.001** | | | |
| SAI | | | | | | | -0.420, p=0.041 | | | |
| TL Errors | | -0.457, p=0.025 | | | | | | | | |
| AER | | | | | | | 0.492, p=0.015 | | | |
| LRU | | -0.412, p=0.046 | | | | | | | | |
| LRR | | -0.439, p=0.032 | | | | | -0.430, p=0.036 | | | |

## Table 3.3 Significant correlations between BIS-11 subscores (columns) and oculomotor task scores.

Values shown are Spearman's Correlation Coefficients (Rho), with 22 degrees of freedom, followed by their statistical significance (2-tailed test).
Value in bold survives Bonferroni correction for multiple (10) comparisons, by adjusting the accepted significance level to $p<0.005$.

*BIS-11: AI= Attentional Impulsiveness; MI = Motor Impulsiveness; NPI = Non-Planning Impulsiveness. RTL £ = Reverse Traffic Light task mean reward; SAI = Mean Stop Anticipation Interval; TL Errors = Mean Traffic Light task Errors; AER = Mean Anticipations:Errors Ratio [Traffic Light Task]; LRU = Lateral Reward Task Mean Unrewarded Saccade Latency; LRR = Lateral Reward Task Mean Rewarded Saccade Latency.*

### 3.3.7 Oculomotor Tasks Correlations (Table 3.4)

As one might predict, there was a significant positive correlation between mean SRT and mean reaction time on the Traffic Light Task, (Pearson's $r(22) = 0.454$, $p<0.05$). Mean SRT also significantly *negatively* correlated with Anticipations:Errors Ratio (AER) in the Traffic Light Task (Pearson's $r(22) = -0.555$, $p<0.05$ (2-tailed)). Thus faster subjects were, on the whole, likely to make more *correct* early responses than slower subjects. Performance on the lateral reward task was similarly correlated significantly with Anticipations:Errors Ratio (AER) in the Traffic Light Task (LRU, Pearson's $r(22) = -0.512$, $p<0.02$ (2-tailed); LRR, Pearson's $r(22) = -0.627$, $p<0.001$ (2-tailed)).

A significant *positive* correlation was between reward obtained on the Reverse Traffic Light Task and the Anticipations:Errors Ratio (AER) in the Traffic Light Task (Pearson's $r(22) = 0.498$, $p<0.02$ (2-tailed)). This suggests that Traffic Light Task performance is dependent upon more than simple saccadic speeding (since anticipatory responding is so highly rewarded). The correlation between a high Traffic Light Task AER and both fast SRTs and high Reverse Traffic Light Task Rewards suggests that there may be common features to optimal performance in both tasks, despite marked differences in the strategies required. In support of this notion, Stop Anticipation Interval (SAI) was significantly negatively correlated with Anticipation/Error Ratio on the traffic light task (Pearson's $r(22) = 0.407$, $p<0.05$). A low SAI requires waiting for *as long as possible* without waiting too long and thereby incurring a penalty. In contrast, a high AER demonstrates the ability to anticipate accurately, and go *as fast as possible* without making excessive early responses (thereby generating too many errors). Correlation between these two measures suggests that the abilities to "wait" for reward under risk and "anticipate" for reward under risk are common traits within individuals.

| *Indicator* | **SRT** | **SAI** | **RTL £** | **AER** |
|---|---|---|---|---|
| **TL RT** | 0.454,<br>p<0.05 | | | |
| **AER** | -0.503,<br>p<0.02 | -0.407,<br>p<0.05 | 0.498,<br>p<0.02 | |
| **LRU** | | | | -0.512,<br>p<0.02 |
| **LRR** | | | | **-0.628,**<br>**p<0.001** |

## Table 3.4 Significant correlations between oculomotor task performance indicators

Values shown are Pearson's Product-Moment Correlation Coefficient (r) with 22 degrees of freedom, followed by their statistical significance (2-tailed test).

Value in bold survives Bonferroni correction for multiple (9) comparisons, which reduces the accepted significance level to p<0.005.

*RTL £ = Reverse Traffic Light task mean reward; SAI = Mean Stop Anticipation Interval; TL Errors = Mean Traffic Light task Errors; AER = Mean Anticipations:Errors Ratio [Traffic Light Task]; LRU = Lateral Reward Task Mean Unrewarded Saccade Latency; LRR = Lateral Reward Task Mean Rewarded Saccade Latency.*

*BIS-11 correlations with TPQ (Table 3.5)*

There were significant *positiv*e correlations between dimensions, factors and total BIS-11 score with dimensions of the TPQ (see Table 3.5).

1) *Positive* correlations were found between BIS-11 Factors/Dimensions and TPQ Novelty Seeking (NS): The Attention Factor correlated positively with NS (TPQ) (Spearman's Rho (22df) = 0.737, p<0.0001). The Motor Impulsiveness (BIS-11) score showed a weaker but still significant correlation with Novelty Seeking (NS(TPQ), Spearman's Rho (22df) = 0.442, p=0.03) as did the Motor Impulsiveness (MI) dimension (Spearman's Rho (22df) = 0.502, p<0.012) and the BIS-11 Total Score (Spearman's Rho (22df) = 0.470, p<0.021). Of these, only the Attention Factor correlation survives adjustment of the accepted significance level to p<0.005 (Bonferroni correction for 10 comparisons).

2) *Negative* correlations were found between BIS-11 Factors/Dimensions and TPQ Harm Avoidance (HA): The Self-Control (BIS-11) Factor *negatively* correlated with Harm Avoidance on the TPQ (HA(TPQ), Spearman's Rho (22df) = -0.611, p=0.001). Similarly, the Perseverance Factor *negatively* correlated with Harm Avoidance on the TPQ (HA(TPQ), Spearman's Rho (22df) = -0.477, p=0.018) as did the Non-Planning Impulsiveness (NPI) dimension (Spearman's Rho (22df) = -0.510, p=0.011) and the BIS-11 Total Score (Spearman's Rho (22df) = -0.596, p=0.002). Of these, the Perseverance Factor and BIS-11 Total Score correlations survive adjustment of the accepted significance level to p<0.005 (Bonferroni correction for 10 comparisons).

3) No correlations were found with TPQ Reward Dependence (RD).

| *Score* | *Attention* | *Motor* | *Self-Control* | *Cognitive Complexity* | *Perseverance* | *Cognitive Instability* | *AI* | *MI* | *NPI* | *Total* |
|---|---|---|---|---|---|---|---|---|---|---|
| NS | **0.737, p<0.0001** | 0.442, p=0.03 | - | - | - | - | - | 0.502, p=0.012 | - | 0.470, p=0.021 |
| HA | - | - | **-0.611, p=0.001** | - | -0.477, p=0.018 | - | - | - | -0.510, p=0.011 | **-0.596, p=0.002** |
| RD | - | - | - | - | - | - | - | - | - | - |

**Table 3.5 Significant correlations between BIS-11 subscores (columns) and TPQ subscores (rows).**

Values are of Spearman's Correlation Coefficient (Rho), with 22 degrees of freedom, statistical significances are for a 2-tailed test. BIS-11: AI= Attentional Impulsiveness; MI = Motor Impulsiveness; NPI = Non-Planning Impulsiveness. TPQ: NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence. Values in bold survive Bonferroni correction for multiple (10) comparisons, by adjusting the accepted significance level to $p<0.005$.

## 3.4 Discussion

### 3.4.1. Findings

We have developed a battery of oculomotor tasks that assesses various components of oculomotor decision-making. The Traffic Light Task (Chapter 2) requires a combination of rapid, reactive saccadic responses and the willingness and motivation to make (highly rewarded) anticipatory responses. However, this must be tempered by avoidance of excessive erroneous responding. The novel and adapted tasks described here allow further exploration of these components.

Mean **SRT task** saccade latency correlated significantly with mean reaction time in the Traffic Light Task. The mean SRT was also significantly *negatively* correlated with the ratio of Anticipations to Errors (AER) in the Traffic Light Task, as were mean saccade latencies in the Lateral Reward task (both rewarded and unrewarded). That is to say faster subjects were, on the whole, likely to make more *correct* early responses than were slower subjects. SRT task performance was not correlated with personality measures (BIS-11 or TPQ), their factors or dimensions.

The **lateral reward task** demonstrated baseline non-significant reward-related speeding of saccade initiation in both young and middle aged volunteers. There was a significant negative correlation between both rewarded and unrewarded mean saccade latencies and AER in the traffic light task. One might expect correlations with SRT task latency, in particular, but this was not found to be statistically significant. These tasks are not identical however: The target in the SRT task is entirely predictable, whereas the Lateral Reward Task demands a response to an unpredictable target, appearing with 50% probability on each side with each trial. Furthermore, saccades are rewarded in the Lateral Reward Task and this may motivate slower responders in the SRT task to respond more quickly, thereby reducing the correlation. Faster SRT responders may already be "at ceiling".

Significant negative correlations were also found between mean latencies and two BIS-11 factors (the motor factor and Attentional Impulsiveness dimension (Table 3.6) – correlations that did not exist for the SRT task. Despite a lack of statistically significant reward-related speeding, it would therefore appear that the Lateral Reward task is sensitive to something more than simple saccadic reaction time, and may be sensitive to reward-related (functional) impulsivity.

The **reverse traffic light task** (RTL) allows insight into subjects' willingness to take risk and is not dependent upon simple motor reaction times. There is no exogenous stimulus to initiate the saccade. The recinormal distribution typical of "reactive" saccadic tasks is not seen. A positive correlation between mean reward in this task and the Anticipation:Error Ratio (AER) in The Traffic Light Task suggests that both tasks are sensitive to mechanisms other than those governing simple reactive saccade generation. Furthermore, this correlation suggests that common qualities, such as sensitivity to reward and willingness to take risk, may be required to perform optimally in both tasks. Reward in the RTL task is significantly correlated with the Attentional Impulsiveness (AI, second order factor) score of the BIS-11. This may reflect the

peculiar task demands that do not require responsiveness to an external saccade-generating stimulus. In support of this reasoning, there is a negative correlation between AI and reward on the Lateral Reward Task, in which paying attention is more beneficial. In this task, where waiting *as long as possible* is rewarded highly, subjects who are less focused on the task, may carry some small advantage.

The inverse relationship between mean SRT and AER in concert with a positive correlation between AER and mean RTL rewards neatly fits with a model of successful traffic light task performance that depends upon a combination of speed, timing, reward sensitivity and willingness to take risk. Oculomotor performance correlations between tasks and with the BIS-11 support the inference that the tasks might be sensitive to impulsivity.

The Cloninger tridimensional personality questionnaire (TPQ) measured similar personality traits and scores correlated with the BIS-11 but not with oculomotor task performance. In light of this, the TPQ was used primarily to screen for novelty seeking tendency in participants of the dopaminergic studies described in chapters 5 & 6 but it was not used for patient experiments.

### 3.4.2 Significance of these findings

Impulsivity can be measured through self-report questionnaires or laboratory based tasks. Despite being used interchangeably, the relationship between these measures is generally small, suggesting that they may measure disparate aspects of impulsive behaviour (Keilp et al., 2005; Dalley et al., 2008; Cyders and Coskunpinar, 2011; Aichert et al., 2012; Cyders and Coskunpinar, 2012). Self-reported impulsivity measures can include sensation seeking, risk-taking, lack of planning, perseverance, and acting on impulses (Whiteside and Lynam, 2001) whereas laboratory impulsivity measures can include inhibitory control tasks assessing the ability to suppress a prepotent response (response inhibition) or a conflicting, competing response (interference control), as well as impulsive choice tasks (e.g. delay discounting) and time estimation measures (Dougherty et al., 2005; Friedman and Miyake, 2004; Nigg, 2000; Robbins et al., 2012).

Behavioural measures can be criticised for employing "sanitised" laboratory presentation conditions that fails to reflect real world pressures upon an individual's decision making (Enticott et al., 2006). Measures using self-report may reflect more stable personality differences and reflect impulsive behaviours over time, whereas lab-based behavioural measures – especially of prepotent response inhibition - can necessarily only measure a "snapshot" of impulsivity through responses made in a discrete time period (Enticott and Ogloff, 2006). The *benefit* of such behavioural measurement, by contrast, is that it allows quantitative measurement of changes in behaviour over time (Keilp et al., 2005), [see also Chapter 4]. Performance measures offer the promise of being sensitive to conditional manipulations, for example reward and/or drug effects, and of providing a quantitative measure of the elemental behavioural tendencies that constitute impulsive traits (Dougherty et al., 2002). We sought to develop a battery of oculomotor tasks that could be used in conjunction with self-report measures in order that we might better establish task outcomes that might *predict* unfavourable outcome behavaiours in those who might not yet rate themselves as impulsive.

Formal psychometric conceptions of impulsivity implicate a number of cognitive factors including attention, reward processing, response inhibition, probability and response selection (Evenden, 1999b; Tzagarakis et al., 2013). Previous studies have demonstrated that oculomotor tasks – particularly those requiring inhibitory control (or prepotent response inhibition) – relate more closely to self-report measures of impulsivity than other behavioural measures such as manual tasks (Jacob et al., 2010; Roberts et al., 2011). We have therefore designed oculomotor tasks that index those cognitive factors thought important in impulsivity.

Ideally outcomes of these tasks would relate to "real-world" behavioural outcomes, better assessed by self-report. BIS-11 scores have previously been associated with both Go/Nogo and antisaccade performance (Spinella, 2004). Associations between BIS-11 scores and Go/Nogo commission errors are frequently reported (Enticott et al., 2006; Keilp et al., 2005; Reynolds et al., 2006). Total BIS-11 impulsivity sum scores have been shown to correlate with tests of prepotent response inhibition (antisaccade, Stroop, stop-signal and Go/Nogo tasks). However, despite a very large number of subjects (n=504), correlations of second-order factors were not found to be significant after correction for multiple comparisons (Aichert et al., 2012). We have demonstrated an association between performances on three rewarded, oculomotor tasks and BIS-11 first and second order factors, one of which is significant after Bonferroni correction. This supports the notion that rewarded oculomotor tasks other than measures of prepotent response inhibition (e.g. antisaccades) can be used to index reward motivated behaviour and impulse control. Further study with greater subject numbers might lead to demonstration of a greater number of significant correlations – including with the BIS-11 total score, as has been demonstrated by other studies e.g. (Aichert et al., 2012).

We might speculatively infer something of the relevant neural mechanisms in our tasks by comparison with other imaging studies that use the BIS-11 and/or oculomotor tasks. The relevance of frontal pathology in diseases known to cause impulsivity is consistent with the finding that various grey matter volumes - including frontal regions - have been found to correlate with total scores and/or subscales of the BIS-11 (Lee et al., 2011; Matsuo et al., 2009). The BIS-11 scale has also been applied in combined behavioural and dynamic (functional) neuroimaging studies e.g. (Horn et al., 2003), thereby enabling further inference about relevant brain areas. A functional imaging study using a Go/Nogo task found negative correlations between the motor impulsiveness subscale of the BIS-11 and Nogo related activation of the right DLPFC (Asahi et al., 2004). This result relates a "stable" BIS-11 personality factor related to real world decision making with a temporally discrete task-related physiology (fMRI BOLD signal) in sanitised laboratory conditions. Furthermore, this finding relates to a brain area thought relevant to oculomotor decision-making (Kim and Shadlen, 1999; Pierrot-Deseilligny et al., 2005; Pierrot-Deseilligny et al., 2003). Moreover, the prefrontal cortex receives reciprocal striatal connections which are likely to be modulated by dopaminergic transmission (Alexander et al., 1986; Daw et al., 2006; Kröner et al., 2007; Leh et al., 2007).

Our findings of correlations between oculomotor task indices (RTL reward, Stop Anticipation Interval (SAI), AER and rewarded saccades in the Lateral Reward task) and the Attentional

Impulsiveness (AI) BIS-11 dimension and, similarly, of correlations between the "Motor" factor of the BIS-11 with an overlapping set of oculomotor outcomes (RTL Reward, Traffic Light Task Errors and saccadic latencies in the Lateral Reward task) suggest that the oculomotor tasks developed here may interrogate important decision-making neural substrates. Further, it suggests that our tasks may be sensitive to changes in brain areas relevant to both oculomotor decision-making and that dopaminergic modulation, whether deliberate (through drug effects) or due to incident pathology, might modulate corticostriatal connections that influence oculomotor decision-making.

This possibility is explored in the remaining experimental chapters of this thesis (Chapters 4-7).

# 4. Dopamine reverses apathy due to focal globus pallidus lesions

I gratefully acknowledge the work of Bogdan Draganski, who performed the diffusion tractography and subsequent imaging analysis described in this chapter, using methods described previously (Draganski et al., 2008).

## 4.1 Introduction

Apathy is a behavioural disorder associated with lack of motivation and reduced spontaneous initiation of actions (Dujardin et al., 2007; Marin, 1991). Although present in mild forms in some healthy people (Lampe et al., 2001), it is a pathological state in conditions such as Alzheimer's and Parkinson's disease where it can have profoundly devastating effects (Chow et al., 2009; Dujardin et al., 2007; Oguru et al., 2010; Starkstein et al., 2006). Understanding the mechanisms underlying apathy is therefore of urgent concern but this has proven difficult because widespread brain changes in neurodegenerative diseases make interpretation difficult and there is no convincing animal model.

Here I present a very rare human case with profound apathy following bilateral, focal lesions of the basal ganglia, with globus pallidus regions that connect with orbitofrontal (OFC) and ventromedial prefrontal cortex (vmPFC) particularly affected. Using two measures of oculomotor decision-making I show that apathy in this individual was associated with reward-insensitivity. However, initiation of responses for higher reward could be established partially with levodopa and more effectively with a dopamine receptor agonist. Concomitantly, there was an improvement in the patient's clinical state, with reduced apathy, greater motivation and increased social interactions.

These findings provide a model system to study a key neuropsychiatric disorder. They demonstrate that reward-insensitivity associated with basal ganglia dysfunction might be an important component of apathy that can be reversed by dopaminergic modulation.

It has long been known that damage to the medial frontal cortex can lead to apathy, with patients demonstrating what is sometimes termed 'abulia': reduced initiation of behaviour, lack of interest in their surroundings and loss of spontaneous emotional expression (Starkstein et al., 2008). A similar state can also occur after focal lesions of the basal ganglia (Bhatia and Marsden, 1994), with the most severe presentations associated with bilateral damage (Laplane and Dubois, 2001; Schmidt et al., 2008). Such cases are relatively rare, however, and although many aspects of their behaviour have been reported, there has been very little experimental study (but see Schmidt et al., 2008) and none have been studied on tests of motivation with dopaminergic modulation.

Here we study one such individual with profound apathy (KD) following focal, bilateral lesions largely involving the globus pallidus of the basal ganglia who provides a rare opportunity to understand both the neurobiology and pharmacological modulation of the condition. We used two oculomotor tasks designed to probe reward-based decision-making. In non-human primates, such behaviour has frequently been studied using eye movements, with globus pallidus neurons demonstrating reward-related activity on such oculomotor tasks (Hong and Hikosaka, 2008; Shin and Sommer, 2010).

## 4.2 Methods

### 4.2.1 Participants

KD was a 41 year-old male referred nine months after suffering simultaneous, ischaemic strokes affecting the internal globus pallidus (GPi) bilaterally 9 months prior to initial testing. KD's lesions involved the GPi on both sides, but with greater involvement on the left where it also affected a small part of the external segment (GPe). They included that portion of the ventral pallidum considered to be within the medial rostral GPi (Haber and Knutson, 2009), but did not extend ventrally below the level of the anterior commissure to affect the subcommissural ventral pallidum region. The ventral striatum as defined in recent human studies (Haber and Knutson, 2009; Mawlawi et al., 2001) was spared, as was the habenula, although of course connections to these regions, including pallidal projections, might well have been compromised.

KD recovered physically within days of his strokes but demonstrated reduced spontaneous and social activity. He reported that friends complained he had become dull, lacking interest in doing anything. He lost his job because of poor performance, but lacked impetus to obtain unemployment benefit. A previously exuberant and outgoing type, he became reticent and reserved, unmotivated even to maintain personal hygiene. He had to move apartment. Despite previously being an earnest music enthusiast, after moving he failed to assemble his hi-fi system because he "couldn't be bothered". He spent most of his day sitting at home, doing nothing.

He did not initiate conversation. Although he was aware of his change in behavior, he seemed to show little concern. Despite demonstrating pronounced apathy, he did not complain of low mood and was not objectively depressed. He denied biological symptoms of depression and did not score within the depressed range on three established scales (Montgomery-Åsberg Depression Rating Scale, Beck and Hamilton rating scales (Beck et al., 1988; Hamilton, 1960; Montgomery and Asberg, 1979). On the Barratt Impulsiveness Scale or BIS-11 (Patton et al., 1995)) KD's score (54) was normal. Verbal and performance IQ were also within the normal range. Neurological examination did not reveal any motor deficits. There were no signs of Parkinsonism. Neuropsychological testing demonstrated normal verbal and performance IQ. KD's main complaint was of lack of interest in others and reduced spontaneity in everyday life. He lost his job and did very little on a day-to-basis, rarely leaving home.

KD's performance on two oculomotor tasks was compared to age-matched controls: Healthy volunteers (13 male, mean age = 41 (SD 5.7); 12 right-handed) completed both behavioural tasks. On the BIS-11 mean total score was 65.3 (SD 11.6). Written consent was obtained from all participants, according to the Declaration of Helsinki.

### 4.2.2 Lesion anatomy, DaT scan and probabilistic diffusion tractography

Structural T1-weighted Magnetic Resonance Imaging (MRI) acquisitions were obtained at 1x1x1 mm resolution (Figure 4.1). Several atlases were used to establish the extent of KD's lesions

(Krauth et al., 2010; Morel, 2007; Prodoehl et al., 2008). Atrophy secondary to degeneration means that there is inevitably some distortion of anatomy, in addition to the lesions themselves. A method adapted from (Draganski et al., 2008) was used to obtain from 12 healthy, age-matched male controls probability maps of projections from pallidum to thalamus in separate cortico-striato-pallido-thalamo-cortical loops. These were then superimposed on KD's lesions in standard MNI (Montreal Neurological Institute) stereotactic space (Figures 4.2-4.5). Lateral orbitofrontal cortex (LOFC) ventromedial prefrontal cortex (vmPFC) and motor cortex (M1) were demarcated according to a recently published method (Desikan et al., 2006).

SPECT (single photon emission computed tomography) imaging of the presynaptic dopamine transporter, $^{123}$I-ioflupane (DaT (Fuente-Fernández, 2012)) revealed good signal bilaterally in the caudate and putamen, demonstrating integrity of the nigrostriatal dopaminergic pathway, one possible locus at which dopaminergic drugs might be able to modulate behaviour. Although it is important to appreciate that dopaminergic receptors are also present in prefrontal cortex which was structurally intact in KD: another potential locus of action of dopaminergic compounds.

### 4.2.3 Traffic Light Task

We used the traffic light task (See Chapter 2) to study KD and his response to dopaminergic treatments. Participants have to anticipate when the light will turn green to obtain high rewards. They fixate a red light (3 degrees diameter) presented for 1000 ms that successively turns amber and then green (See Chapter 2) which is the signal to make a saccade to a target cross at 20 degrees horizontal eccentricity. Amber duration is not fixed but drawn probabilistically from a Gaussian distribution (mean 750ms, SD 125ms; see Chapter 2). Rewards on this task depend upon saccadic latency, with very fast responses given very high rewards (according to an exponential discounting function; see Chapter 2). But saccades made before the green light were penalized with a small, flat penalty.

Because saccades take ~200 ms to initiate (White et al., 1962), any highly rewarded responses (latencies <200 ms) have to be programmed before the amber light turns green. Thus to maximize outcome, subjects need to anticipate when the amber will turn green, but not make a response beforehand. They need to make a decision about whether to initiate a response before the green light – and potentially obtain a high reward, but risk a penalty – or simply wait for the green light when they will receive a low reward, without risk of penalties. Participants were instructed to make as much money as possible. They performed ten blocks of fifty trials, the first trial in each block started from a left sided stimulus (rightward saccade) and then alternated. In order to characterize learning effects, a subgroup of six aged matched controls performed a further ten blocks of fifty trials in a repeat experimental session.

The reward ($R$) for a successful saccade was calculated by an exponentially decaying discounting function in the form:

$$R = ae^{-\left(\frac{t-t_0}{k_1}\right)}$$

Where $a$ = 150, $k_i$=100 and $t$ represents the saccade onset time relative to green onset ($t_0$, milliseconds).

Saccades made in advance of the "Go!" signal were punished by a fixed negative reward of -10 pence (10p). Rewards were displayed at the arrival site on each trial and a cumulative total was shown below this. Aural feedback was also given with a pleasant 'ping' for rewards of 0-19 p, and a more rewarding 'ker-ching' for rewards of 20p or more. A punished error trial was accompanied by a low-pitched 'beep' in addition to a visual cue that read, "STOP Police! Fine £0.10". Eye position was recorded using an EyeLink 1000Hz eye tracker (SR Research Ltd, Ontario, Canada). The stimuli were displayed on a 22" CRT monitor (150Hz) at 60cm.

*Linear rise-to-threshold modelling*

It is not possible to establish definitively for any individual correct saccade whether or not it arose from an anticipatory or a reactive process. Because humans take ~200ms to plan and execute saccades in response to a visual cue, 'reactive' saccades – those made in response to green light onset – would be expected to have latencies of this order. Very early saccades (say <50ms after green onset) are likely to have been planned prior to green onset. However, there is a 'grey area' between these extremes. We therefore need a method to decide how many of the saccades were s*tatistically most likely* to arise from each distribution.

Saccadic distributions have been well modelled by a linear rise-to-threshold process (Carpenter and Williams, 1995). We assumed two such processes, one triggered by the amber light and the other by the green. Thus, a rapid rise-to-threshold process elicited by green light onset would describe the distribution of reactive saccades. Whereas *a slower, independent rise-to-threshold process describes anticipatory saccades* triggered by *amber* light onset. According to this scheme, a saccade is generated by whichever process is first to reach threshold (Adam et al., 2012).

The probability that a saccade has occurred by time $t$ following amber onset (i.e. cumulative probability distribution) is described by:

$$\Pr(T \le t) = \Psi_A(t) + \Psi_R(t - t_0) - \Psi_A(t)\Psi_R(t - t_0)$$

$\Psi_A$ and $\Psi_R$ indicate cumulative recinormal distributions describing anticipatory and reactive processes, respectively. Each distribution is parameterized by a mean ($\mu$) and variance ($\sigma^2$) of the rate-of-rise, and defined in terms of the standard cumulative normal distribution $\Phi$ as follows, for $t > 0$:

$$\Psi_{\mu,\sigma^2}(t) = 1 - \Phi\left(\frac{1/t - \mu}{\sigma}\right)$$

We used maximum likelihood estimation (Myung, 2003) to obtain best-fitting mean and variance parameters for each distribution. When applied to the combined data from all controls, the model estimates a mean for the reactive distribution of 299m, SD 31ms. We used a 'cut off' maximum saccadic RT of 200ms, >3 SDs from the mean of the modelled reactive distribution, to count *anticipatory* saccades. Even when modelled individually, 200ms was a minimum of 2 SDs below the modelled reactive mean for each control subject.

### 4.2.4 Lateral Reward Task

We also tested participants on the lateral reward task (Chapter 3), a simple tool for assessing reward sensitivity. The subject is asked to fixate a central spot for 1000ms before making a saccade to a target which appears 10 degrees to the right or left (50% probability on each trial). Participants quickly learn that one side is rewarded whereas the other side is not, and normally reward sensitive individuals make faster responses to the rewarded side. Rewarded trials were acknowledged by the display of a pound coin and a number representing the magnitude of the reward in pence. Reward value was dependent on latency using a function similar to that in the traffic lights task. A red circle and a zero acknowledged unrewarded trials. The rewarded side changed every 10-14 trials. Participants performed two blocks of 120 trials, with a subgroup of six aged matched controls performing a repeat of these two blocks in order to investigate learning effects. The difference between the reaction times to the rewarded and unrewarded sides was taken as a measure of a subject's sensitivity to reward as it reflects the modulation of behavior by reward.

### 4.2.5 Dopaminergic drug challenges

To investigate the effect of dopamine, KD received a single dose of levodopa in the form of Madopar 125 mg (100 mg L-dopa with a peripheral dopa-decarboxylase inhibitor, benserazide 25mg), directly after performing the baseline tests. He was reassessed an hour later when peak levodopa levels were reached. Control participants also received the same drug dose but in a double-blinded, randomized fashion, so on one occasion they received placebo/drug and one week later they received the alternative.

KD was then given slowly increasing doses, reaching Madopar CR (long acting preparation) 125mg three times daily after eight weeks. Although there was moderate improvement in apathy, it was decided that there might be better response with a direct dopamine receptor agonist. L-dopa was therefore slowly discontinued and KD was off medication entirely for 4 weeks ('drug holiday') before starting on the dopamine agonist ropinirole, initially 0.25 mg three times a day for 1 week, then increasing by 0.25 mg every week eventually to reach 1mg thrice daily after three weeks. After a further four weeks he was established on 4 mg once daily of the long-acting formulation of ropinirole (Requip XL).

## 4.3 Results

### 4.3.1 Lesion anatomy and probabilistic tractography data

KD's lesions (Figures 4.1-4.3) involved the GPi bilaterally, with greater involvement on the left where it also affected a small part of the external segment (GPe). Using a recently validated atlas of the pallidum (Prodoehl et al., 2008) we found only modest damage to GPe on the left. There was no involvement of the habenula, subthalamic nucleus, septum, medial hypothalamus, midline thalamic nuclei, and bed nucleus of *stria terminalis*, verified using a MRI adapted version (Krauth et al., 2010) of the Morel histologically-based atlas (Morel, 2007). Probabilistic diffusion tractography was used to examine the topography of pallidal connections to cortex, via thalamus (Draganski et al., 2008). Probabilistic diffusion tractography (Figure 4.4) was used to examine the topography of pallidal connections to three cortical regions (Draganski et al., 2008). The region of GPi which is most strongly connected to lateral orbitofrontal cortex (LOFC) and ventromedial prefrontal cortex (vmPFC) was particularly affected, compared with projections to primary motor cortex (M1), more so on the left: vmPFC > M1 left $Z = 5.41$, right $Z = 3.51$; LOFC > M1 $Z = 5.33$, right $Z = 3.52$ (all $p < 0.001$, uncorrected).

### 4.3.2 Oculomotor baseline performance

On the traffic lights task saccadic latencies in controls demonstrated a bimodal distribution (Figure 4.5). One population of saccades consisted of late responses with a peak distributed ~280ms after green onset, consistent with eye movements made 'reactively' in response to the GO Signal. In addition, there was a population of early saccades with a peak at 63ms after green onset. These saccades are too fast to have been made in response to green onset and therefore correspond to eye movements programmed beforehand.

To demarcate these two populations of saccades – anticipatory and reactive – we used linear rise-to-threshold modelling, assuming two independent processes, the first triggered by amber light onset and the second by the green light. The early, anticipatory responses can be further sub-divided into errors (eye movements before green onset) and correct anticipations (saccades after green onset, but planned in advance of it). A criterion of 200 ms was employed as a cut-off for correct anticipations (see Methods). Responses after this time were classified as 'reactive' saccades.

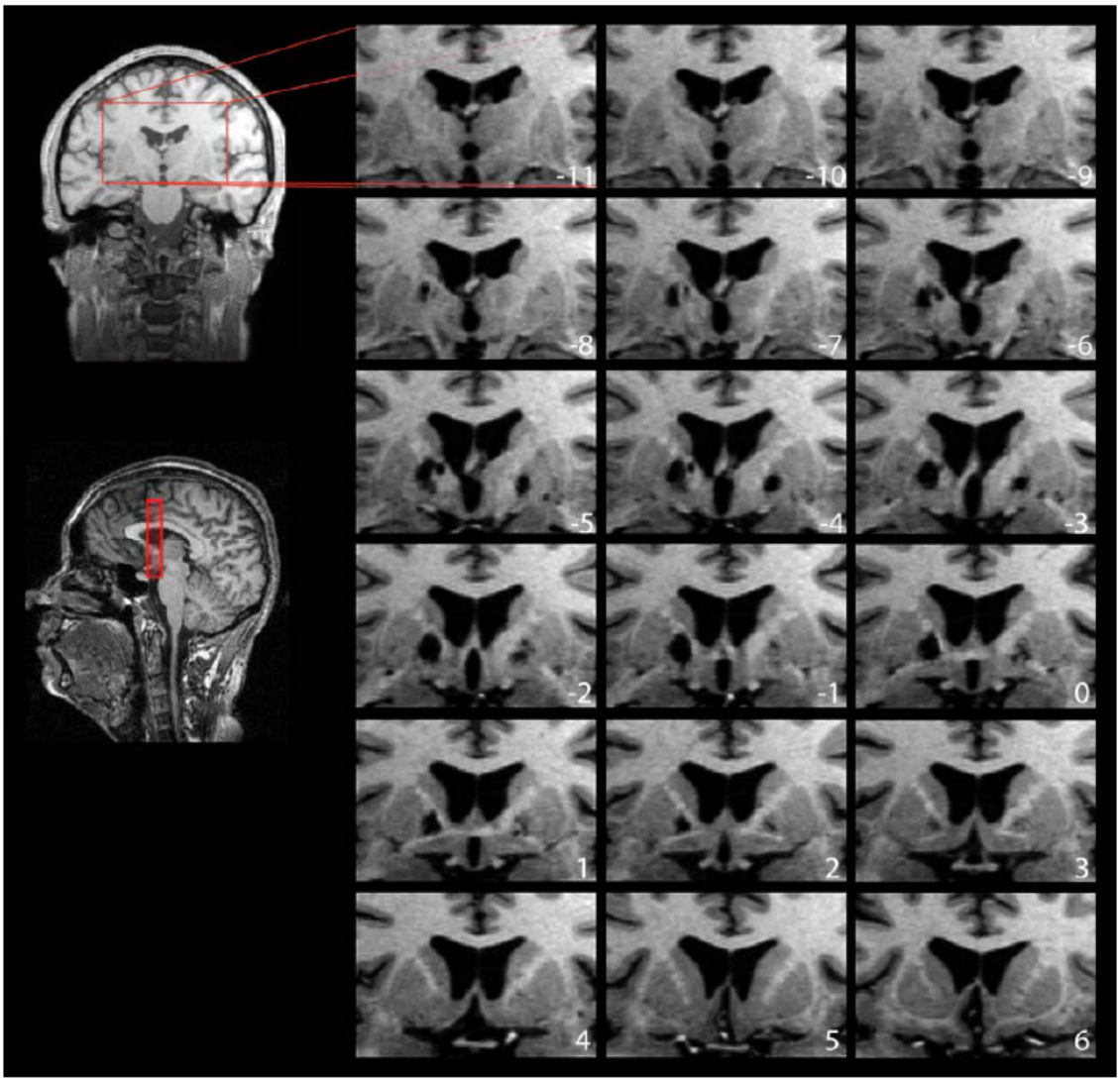



**Figure 4.1 KD's Pallidal Lesions**

Coronal T1 weighted Magnetic resonance Images of KD's brain demonstrate the extent of his bilateral GPi lesions. The slice labelled zero corresponds to the anterior commisural plane, with positive values anterior to this and negative values showing slices posterior to this level.

A

B

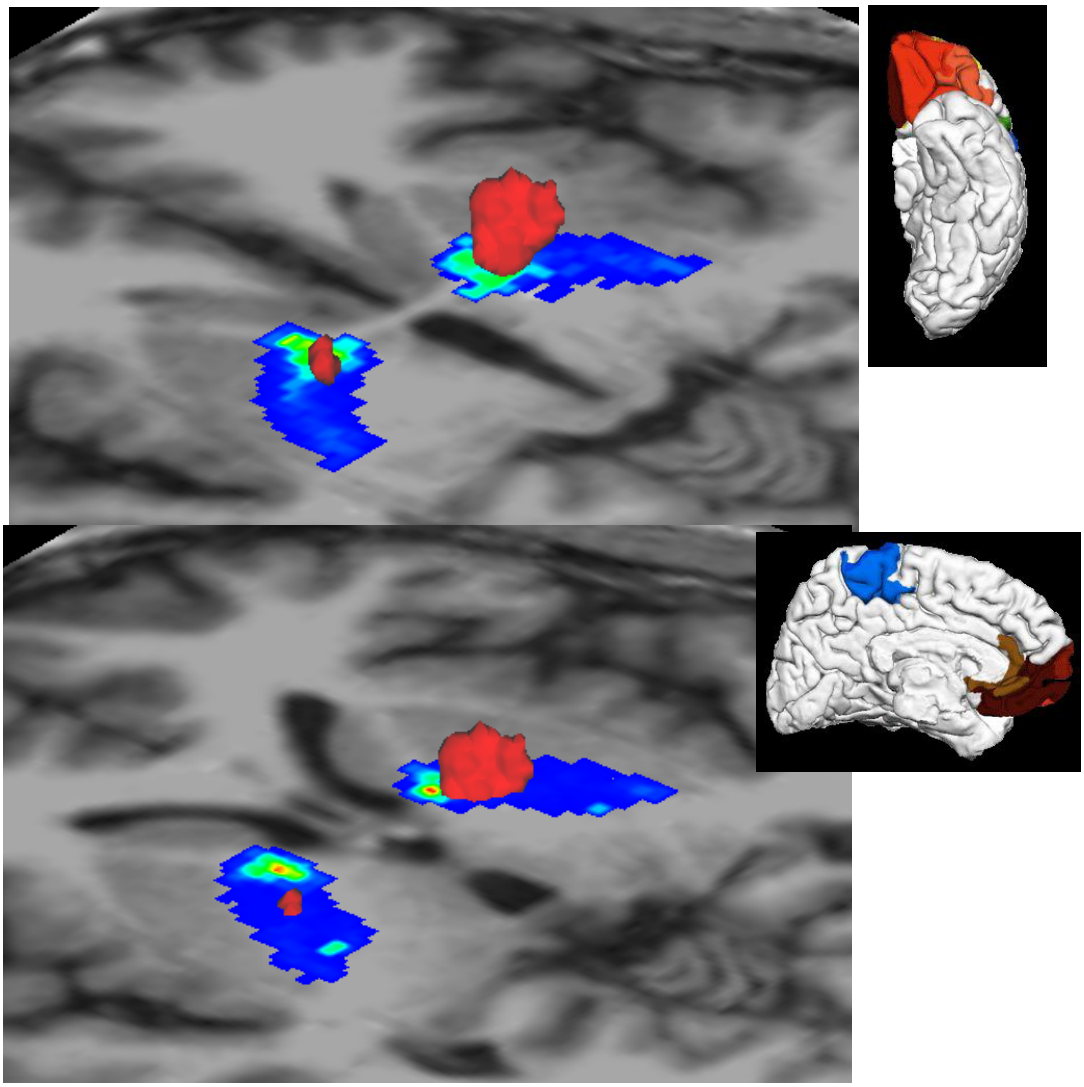


**Figure 4.2 Lesion Mapping**

The patient's pallidal lesions are shown as 3D volumes in red and have been superimposed on connectivity-based probability maps derived from 10 healthy, age-matched male controls. The control subjects' connectivity maps for the pallidum-thalamus-orbitofrontal cortex loop are shown in A with the cortical target area shown in red and orange in the inset (figure modified from Draganski 2008). Those for the pallidum-thalamus-M1 cortex loop are shown in B (blue cortical region in the inset). The jet coloured scale indexes group average connectivity probabilities for the two loops, with "hot" colours indicating higher probabilities. The centre of mass for pallidum-thalamus connections to orbitofrontal cortex is contained within the lesion (A), while those to M1 are not (B). The images are rendered into standard MNI (Montreal Neurological Institute) stereotactic space.

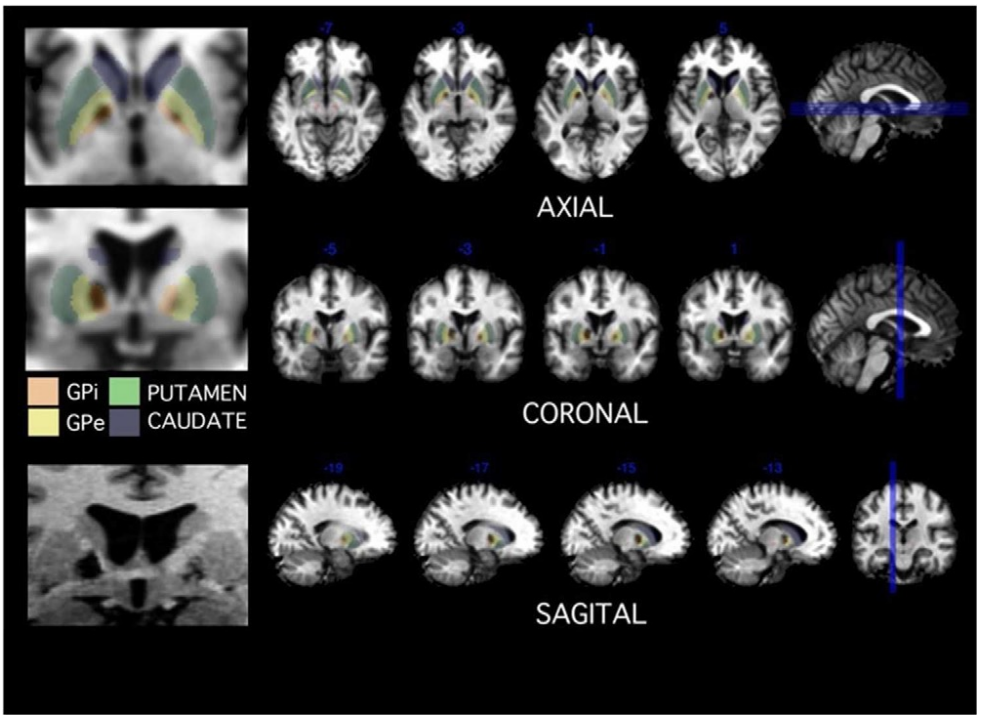



**Figure 4.3 KD's GPi lesions projected onto anatomical boundaries of basal ganglia.**

KD's GPi lesion was larger on the left than on the right. The lesions are projected onto boundaries of the GPi (orange), GPe (yellow) and putamen (green).

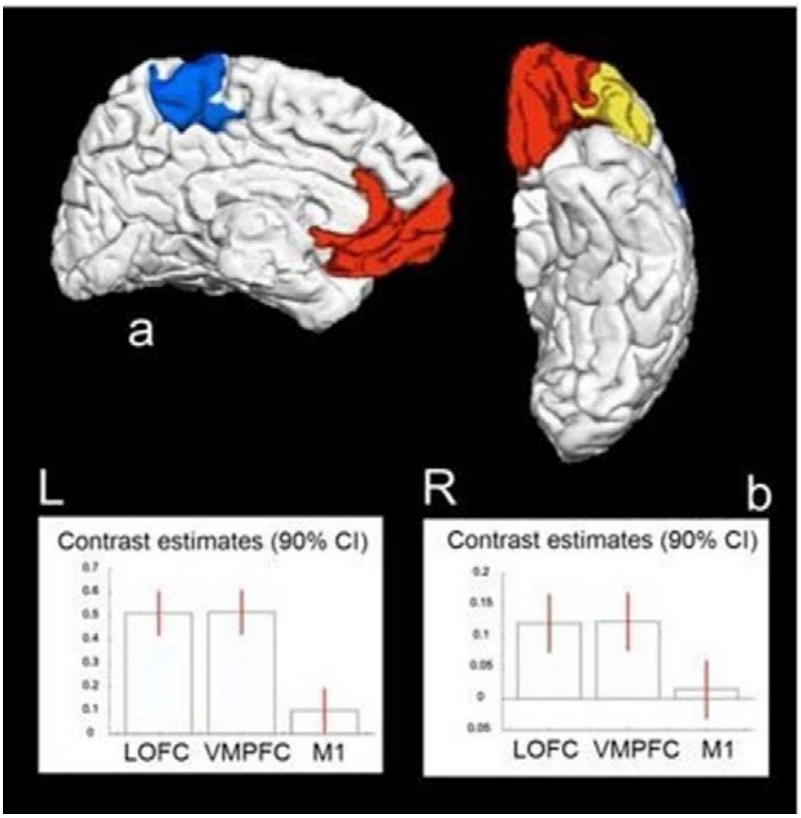



**Figure 4.4 Lesion location in relation to pallido-thalamo-cortico projections.**

a) For DTI analysis, three cortical sites are shown: LOFC (yellow), VMPFC (red) and M1 (blue).

b) Regression coefficients (betas) extracted from the voxel of maximum intensity within the lesion on the left (L) and right (R) for the three tracts. High values indicate that the tract passes through the lesion with a high probability.

Using this cut-off, controls demonstrated a high proportion of early responses (mean 42% saccades, SD 18.95). Half of these were correct anticipations (21% saccades, SD 8.64). The rest were errors, i.e. early responses before the green light (21% saccades, SD 14.35). Overall the mean correct Anticipations: Errors Ratio [AER]) for controls was 1.53 (SD 0.87), with mean reward 18p/trial (SD 4.6p). AER correlated well with mean reward obtained ($R^2$=0.77; p<0.0001). In contrast, KD's distribution of saccades was unimodal, with the majority of responses being made only after green light onset (Figure 4.5). Nearly all his eye movements were reactive, with only 8.0% being early responses, significantly different from controls (Z=2.8, p=0.003). Furthermore, the majority of these were errors; correct anticipations formed only 2.2% of saccades (Z=2.8, p=0.003). His AER was 0.4 and he obtained only 14p/trial.

Analysis of learning showed that controls gradually increased the proportion of early responses such that there was a significant difference between the first epoch of 100 trials (30.5 % early responses, SD 25.20) and the third epoch of 100 trials (44.6 % saccades, 21.24) (p = 0.0271). A subset of six aged matched controls performed a second session (a further 500 trials) to check whether there is any ongoing learning. The proportion of early responses in these subjects remained relatively constant from the end of the first session (45%) to the end of the second session (48%) with no significant difference to suggest further learning (p >0.1). In contrast to controls, KD showed no learning with 8% early responses in the first 100 trials to 7% early responses in the last 100 trials (Figure 4.6). On the lateral reward task healthy age-matched controls showed a small, but significant saccadic reaction time (SRT) advantage to the rewarded side (mean RS 206 ms vs. US 219ms; p=0.03). Interestingly, this sensitivity to reward, (difference between US and RS) did not change significantly over time (learning analysis of three forty trial epochs F(5,66)=0.24, p = 0.9449, additionally six subjects performed a further repeat session demonstrating no learning F(11,60) = 0.7, p 0.7349.) By contrast, KD showed no significant difference between latencies for rewarded (RS) compared to unrewarded saccades (US) (mean US = 236ms vs. RS = 235ms; p>0.5; Figure 4.7, Session 1). KD's reaction times were longer than the control means but within the normal range. Thus, at baseline, on this simple lateral reward task, he displayed reward dependent behavioural modulation suggesting indifference to rewards. KD also did not show any significant change in his performance within session across epochs.

### 4.3.3 Dopaminergic modulation of oculomotor performance

On the traffic lights task KD's performance altered dramatically one hour after a single dose of L-dopa 100mg (Figure 4.6). His early responses increased (26%), with a AER of 4.20 ( 6.67 SD greater than control mean of 2.20, SD 0. 0.30). There was an overall increase in reward to 18.4p/trial. The same dose of L-dopa in 12 controls, tested in double-blind fashion, had no significant effect on saccadic RTs, AER or reward (See Chapter 5). Thus a single dose of L-dopa increased anticipatory saccades in KD but not in healthy people. Learning analysis showed post L-dopa, KD sharply increased the proportion of early responses (14% in first one hundred trials post L-dopa to 43% in trials four hundred to five hundred). This was the largest increase in the percentage of early responses of any subject either at baseline or with L-dopa (Fig 4.6).

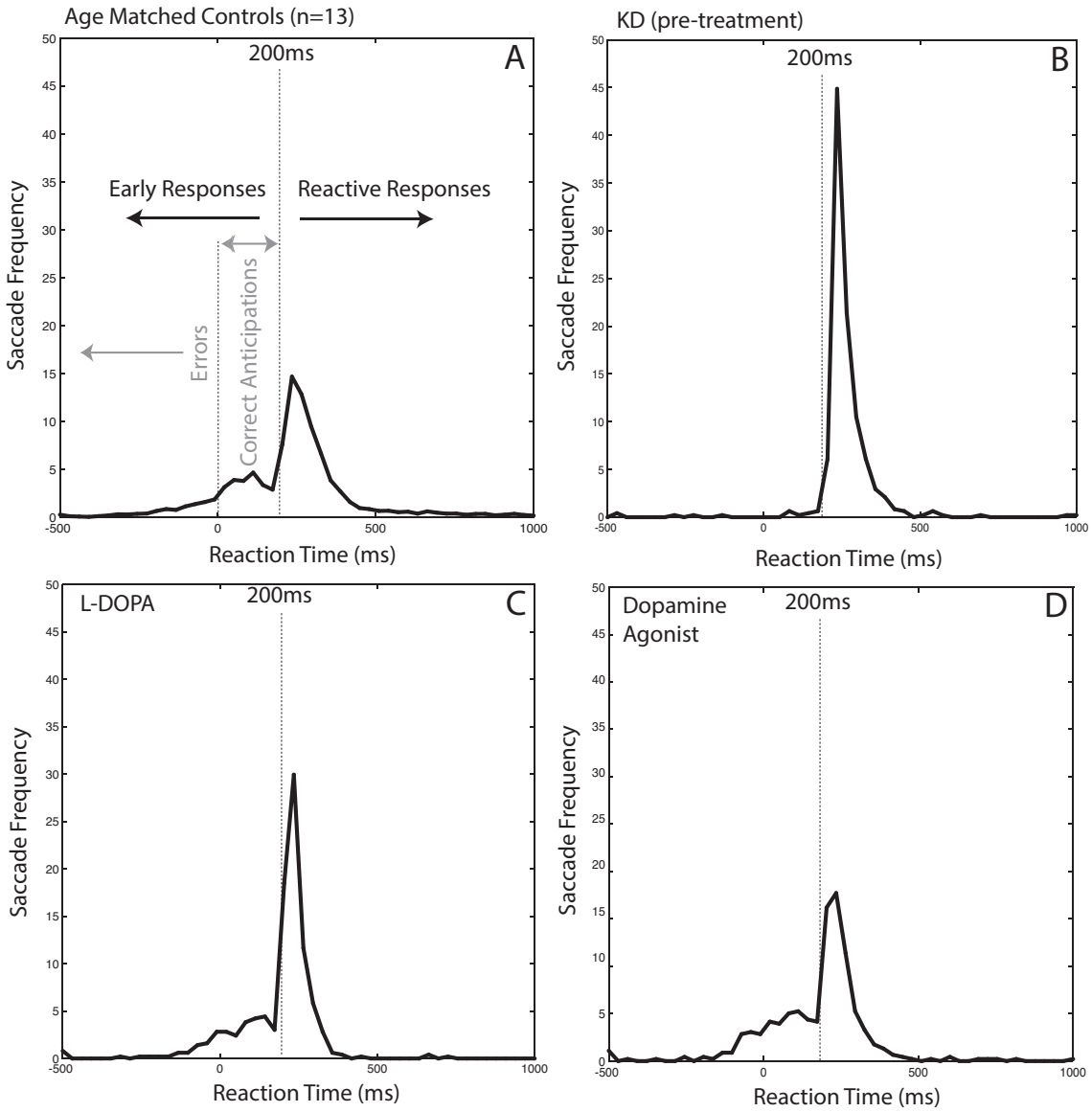



**Figure 4.5 Traffic light task (TLT): saccade distributions.**

(A) Saccades for age-matched controls (n=13) performing the TLT two distinct distributions: an early, anticipatory distribution and a later, reactive one made in response to green light onset. Early responses were divided into errors (saccades before the green light came on) and correct anticipations (saccades with<200 msec latency after the green light). The plot here is for a total of 6500 saccades.

(B) Pre-treatment, KD made mostly reactive saccades (461/500 trials [92.2%]) with a median latency of 248 msec. He made very few anticipatory saccades.

(C) After treatment with L-dopa 100 mg (Madopar CR 125 mg) three times a day for 12 weeks, there was a dramatic increase in early responding in KD.

(D) After 12 weeks treatment with a dopamine agonist (ropinirole XL, 4 mg once a day), KD's distribution of saccades looks most similar to that of control subjects.

On the lateral reward task, following L-dopa, KD showed a markedly significant preference for the rewarded side (RS 211 ms vs US 238ms; p=0.002). Eight healthy volunteers tested in double-blind fashion on the same dose of levodopa or placebo demonstrated reward sensitivity, as previously but, importantly, there was no further significant modulation by L-dopa. Thus L-dopa speeded saccades to rewarded targets in KD but not in healthy people. After eight weeks on levodopa, KD showed moderate behavioural improvement in apathy. Concomitantly, the difference in saccadic RT to rewarded and unrewarded targets was much larger than in healthy controls, a consistent finding across all testing sessions (Figure 4.7). Twelve weeks after initiating therapy, the difference between rewarded and unrewarded saccades was 36 ms (RS = 206ms vs. US = 242ms; $p<0.0001$). In isolation, these findings might be attributed to practice. However, saccadic RTs to unrewarded targets actually increased while those to rewarded ones decreased, so the effects cannot be attributed to a simple generalized motor facilitation with practice and/or L-dopa.

On the traffic lights task, performance reached a peak by 24 weeks therapy when 33.4% of KD's saccades were now early responses, with 23.6% correct and 9.8% errors (AER=2.41 and mean reward now 23.2p/trial).

A clinical decision was made to stop L-dopa and assess instead the effects of a dopamine agonist that acts directly at dopaminergic receptors, rather than indirectly by promoting dopamine synthesis. Off medication, the difference in SRTs to rewarded and unrewarded targets became non-significant (Figure 4.7), providing further evidence that the reward-sensitivity observed in the previous sessions could not simply be attributed to practice. On the traffic lights test, off medication, the effects on L-dopa were also partly reversed with overall reward dipping to 13.7p/trial and AER=0.79.

KD was then started on an increasing dose of ropinirole, an agonist acting largely D2 and D3 dopamine receptors, rather than D1. By contrast, L-dopa would have a balanced effect across all these receptors by increasing synaptic dopamine levels. On 4mg ropiniorole daily there was marked improvement in KD's apathy. He was far more spontaneous in conversation, reported better social interactions and was more interested in events around him. He managed to secure a job. On the lateral reward task, saccades were generally faster, but those to the rewarded side were significantly faster than to the unrewarded side (RS = 183ms vs. US =208ms; $p<0.001$), far larger than in controls.

On the traffic lights task, by week four (on 4mg ropinirole daily) KD demonstrated much greater early responding (45.2%). However, this was at the expense of greater numbers of errors (17.8% vs. control mean = 24.2%) so the AER (1.54) was not as high as on L-dopa (0.96 SD above control mean). Despite this, his mean reward exceeded that achieved on L-dopa, with a mean trial reward of 27.3p/trial, matching the highest performing individual healthy control. Thus KD showing increased willingness to anticipate frequently and take risks, an effect that persisted over 12 weeks on ropinirole (Figure 4.7).

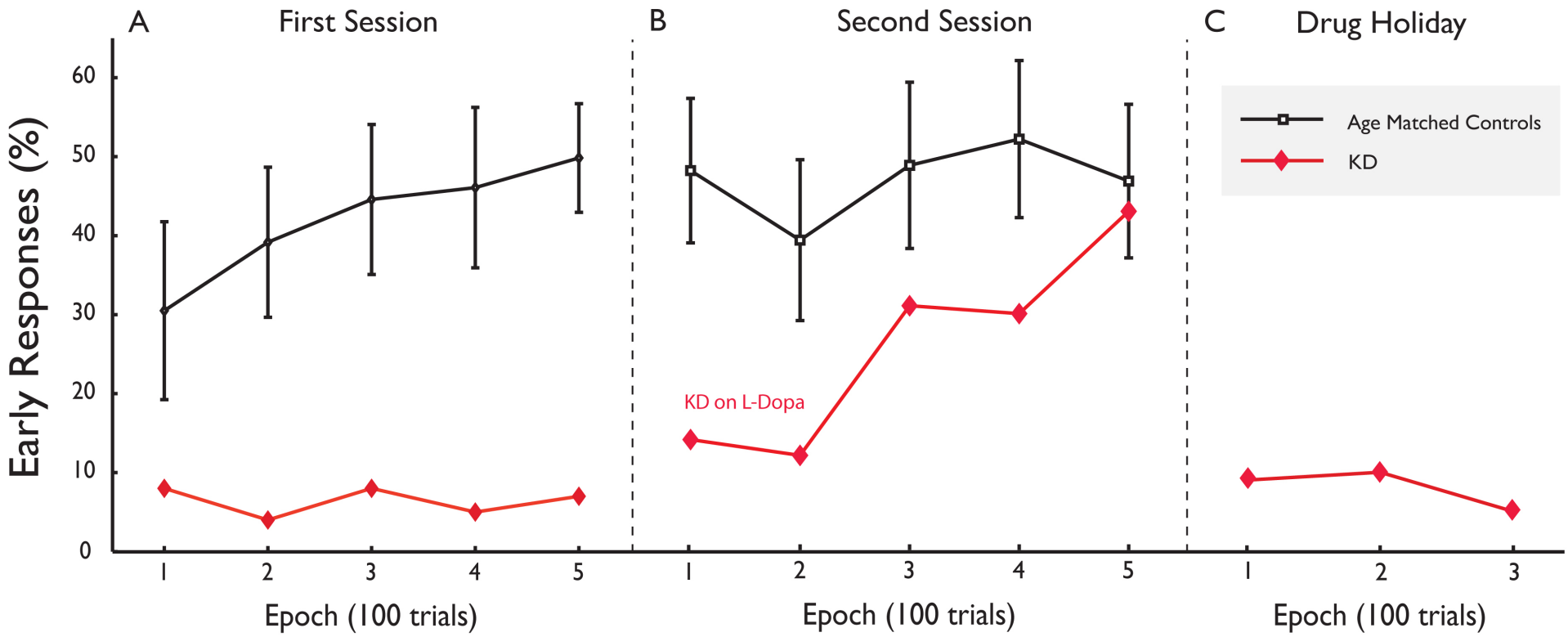



**Figure 4.6** **Percentage early responses on traffic lights task (TLT) over time.**

**A** Over the course of the first session, healthy controls showed increased early responses but KD did not.

**B** In the second session, an hour later, controls showed no further change but KD 1 h after receiving L-dopa showed escalating early responses.

**C** During the drug holiday period (off L-dopa), KD's early responses reverted to pre-treatment levels.

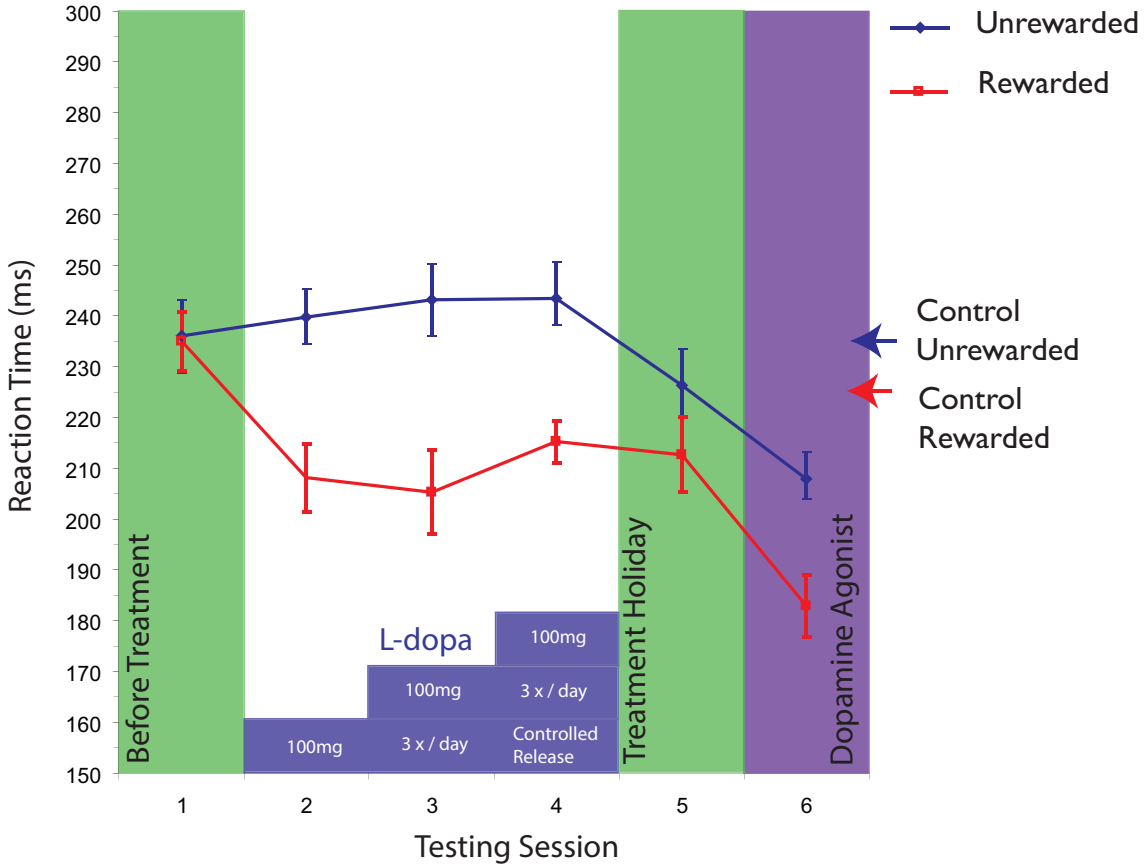



**Figure 4.7 Results from the lateral reward task.**

The control group (n=12, arrows to side) showed a preference for the rewarded target locations, with significantly shorter SRTs. KD showed no reward preference at baseline, before treatment (Session 1). In Session 2 he was given a single dose (100 mg) of levodopa which led to a significant reward preference. This was maintained throughout chronic dopaminergic therapy (Session 3 Madopar 125 mg three times daily for 4 weeks, Session 4 Madopar CR 125 mg three times daily for 12 weeks). Following a treatment holiday (4 weeks), this reward preference was absent (Session 5). However, with subsequent treatment on the dopamine agonist ropinirole (1 mg three times a day), there was both a re-establishment of reward preference and significant decrease in latency to both rewarded and unrewarded targets. Error bars are ±1 SEM (standard error of the mean).

## 4.4 Discussion

### 4.4.1 Findings

I have used novel probes of oculomotor decision-making to demonstrate relative insensitivity to reward in an individual with apathy following bilateral GPi lesions. The traffic light task (TLT, Chapter 2, (Adam et al., 2012)) requires reward sensitivity and motivation or effort to succeed, combined with fast reaction times and the ability to update behaviour in response to positive and negative feedback. A reactive response - simply waiting for the green light - is less well rewarded than an anticipatory response prepared in advance of the green signal.

KD initially made very few anticipatory responses compared with age-matched controls. However, dopaminergic therapy, first with levodopa and then with ropinirole, increased anticipatory responses to within the normal range. The directional saccade lateral reward task, originally developed for the study of reward sensitivity in macaque monkeys (Hong and Hikosaka, 2008), demonstrated that KD had SRTs within the normal range but showed no speeding to the rewarded side (RS), unlike healthy volunteers. Treatment with levodopa led to reward sensitivity, with speeding of responses to the RS and slowing to the unrewarded side (US) compared to baseline. Off medication, the difference in SRTs to rewarded and unrewarded targets became non-significant, while subsequently on ropinirole, a direct dopamine D2/D3 receptor agonist, KD again demonstrated reward sensitivity, as well as generalized speeding.

These effects on dopaminergic medication were associated with clinical improvement, reduction of apathy and increased motivation to find work and in social interactions – most prominently while on the dopamine agonist. The findings demonstrate a causal relationship between basal ganglia function and motivation or willingness to make an effort for reward. They provide proof-of-concept data for the treatment of apathy which is increasingly recognized to be a key component of several neurological disorders (Marin, 1991; Bonelli and Cummings, 2008; Chow et al., 2009; Starkstein et al., 2009).

### 4.4.2 Significance

Unlike other tasks involving risk, such as the Iowa Gambling Task or the Cambridge Gamble Task (Clark et al., 2004), the TLT requires participants to take risks by making anticipatory responses. Many other paradigms place certain and risky options on an equal footing with the same amount of effort required for both choices. This has the benefit of establishing risk preferences independently of effort but tends to favour a careful, deliberative response strategy. The traffic lights paradigm imposes time constraints on decisions and rewards behaviour that might be considered 'functionally impulsive' (Dickman, 1990): on this task, it can be functionally useful to make anticipatory responses because these can lead to greater rewards, analogous to many situations in real life.

It is possible that KD's lack of anticipatory responses on this task reflects risk aversion, rather than lack of motivation or unwillingness to make an effort for rewards. However, it is less easy to explain how such a mechanism might account for behaviour on the lateral reward task, where there was no risk of incurring a penalty. How did dopamine reverse apathy and reward

insensitivity? Substantial evidence links dopamine to reinforcement learning (Schultz, 2007). However a growing body of research also implicates dopamine in effort-based decision-making, generating the motivation and vigour to overcome costs of initiating actions (Kurniawan et al., 2011; Niv et al., 2007). The progressive improvement of KD's performance on the TLT immediately post L-dopa (Figure 4.6B) is suggestive of dopaminergic enhancement of learning. However, during the drug holiday period such learning was radically reversed (Figure 4.6C), suggesting that if this effect was solely due to a reinforcement learning effect of L-dopa it had not been completely consolidated. Dopamine was still required to maintain it.

On the directional lateral reward task, L-dopa also had a dramatic effect after its introduction, speeding saccades to the RS (Figure 4.7). During the drug holiday, however, there was no longer any significant reward-sensitivity but saccades were generally faster than before treatment, suggesting there were some general, non-specific effects of practice on the task. The time course of action on reward-sensitivity and its reversal during the drug holiday makes it unlikely that dopaminergic effects on synaptic plasticity and learning were the only mechanism of action. Instead, it might also have had an effect on response vigour or overcoming costs of effort actions (Kurniawan et al., 2011; Niv et al., 2007).

Dopamine could act directly on brain systems left intact after stroke, but perhaps disconnected because the major outflow from the basal ganglia is via the globus pallidus (GP). Alternatively, because the GPi lesions were not complete in KD, it is possible that his lesions led to imbalance in cross talk between striatal regions, which could be ameliorated by dopamine therapy. It has been demonstrated that parallel corticostriatal loops through the basal ganglia need not operate in isolation but can instead communicate with each other, e.g., via spiralling striato-nigro-striatal connections (Haber et al., 2000) which allow ventral striatal regions to influence more dorsal striatal areas. Moreover, the nigrostriatal system is not the only dopaminergic modulator of basal ganglia function; the intra-striatal dopaminergic system is complex and can alter with denervation (Smith and Kieval, 2000). Finally, it is important also to consider the possibility that the effects of dopamine observed in KD might arise from indirect, knock-on effects on other neurotransmitter systems, e.g., there is evidence of interactions between dopaminergic and noradrenergic systems (Hara et al., 2010) as well as several other neurotransmitters ((Steiner and Tseng, 2010)).

In macaques, using the directional reward saccade task, Hong and Hikosaka (2008) found that saccades to the RS with shorter latency than to the US, with reward-related speeding being associated with activity in GPi neurons which project to the lateral habenula. If a homologous circuit operates in the human brain, it is likely to have been partially disrupted in KD in whom both GPi were damaged. However, the lateral habenula remained intact, together with the caudate and putamen.

Furthermore, SPECT imaging of the DAT demonstrated that the nigrostriatal dopaminergic pathway was intact as there was good signal bilaterally in the caudate and putamen of KD. Thus one locus of dopaminergic drug action is potentially the intact caudate, putamen or even surviving parts of the GP complex. Another potential site of action of dopamine is prefrontal

cortex. The OFC, in concert with basal ganglia structures, is considered to have a special role in the processing of reward signals (Kringelbach and Rolls, 2004; Schultz, 2000; Schultz et al., 2000; Wallis, 2007). Projection of KD's lesion onto the known topography of the pallidal trans thalamic connections to the cortex, determined using diffusion-weighted tractography (Draganski et al., 2008), suggests that the connections to the vmPFC and OFC have most likely been disrupted (Figure 4.4). OFC neurons not only respond selectively to reward or aversive stimuli, but also signal relative preference for rewards and may integrate different types of information to compute a representation of value (Padoa-Schioppa and Assad, 2006; Thorpe et al., 1983; Tremblay and Schultz, 1999; Wallis and Kennerley, 2010).

Consistent with these neurophysiological findings in macaque monkeys, imaging studies in humans have described activations in OFC and vmPFC which correlate with behavioural measures of stimulus value (O'Doherty, 2004; Blair et al., 2006; Plassmann et al., 2007; Gläscher et al., 2009; Haber and Knutson, 2010; Rangel and Hare, 2010). Lesions of the OFC in humans lead to impaired decision-making about the expected outcome of choices (Bechara et al., 1998) while alterations in striatal dopamine binding in drug addicts is associated with hypoactivity in OFC (Volkow et al., 2009). Dopaminergic neurons are known to innervate prefrontal cortex, including OFC (Williams and Goldman-Rakic, 1993). Although these arise from midbrain dopaminergic populations, partial disconnection of OFC neurons from trans-thalamic pallidal inputs - as is likely in KD -might disrupt dopaminergic reward signals within OFC. This view is compatible with recent functional imaging evidence that dopamine agonists might alter decision-making and risk-taking in susceptible individuals with Parkinson's disease via actions on OFC (van Eimeren et al., 2009).

Intriguingly, previous work also suggests that a dopaminergic deficit might be an important contributory factor to apathy in Parkinson's disease, which occurs in up to 60% of cases (Oguru et al., 2010). Patients who undergo STN deep brain stimulation (DBS) often require reduction or withdrawal of dopaminergic therapy because of improvements in motor control following surgery. Czernecki et al. reported that apathy occurred after dopamine withdrawal in some of these cases, but importantly it could be reversed with ropinirole (Czernecki et al., 2008).

More recently, a PET study has demonstrated greater meso-corticolimbic dopaminergic denervation involving the OFC in Parkinson's disease patients who develop postoperative apathy compared to those who do not (Thobois et al., 2010).

Regardless of the precise locus of drug action in KD, it is clear that his lesions rendered him apathetic but this could be ameliorated by dopaminergic modulation. Alteration in reward-sensitivity mirrored clinical changes, suggesting that apathy in this case is associated with lack of motivation to obtain rewards. Animal learning theory has proposed that rewards might in fact constitute the basic goals of voluntary behaviour (Dickinson and Balleine, 1994). From this perspective, the absence of sensitivity to rewards would be expected to have devastating consequences for goal-directed action, just as one observes in apathy. But note that although this view might account for behaviour in our particular case, apathy is most likely to be a syndrome that is multidimensional (Cummings, 1993; Levy and Dubois, 2006). In different

clinical contexts, it could potentially result from deficits in other cognitive components of the decision-making process. Further studies are required to delineate these components and which specific deficits occur in different clinical conditions. Our study represents progress towards understanding one component of apathy-namely, relative reward insensitivity.

Although cases such as KD with bilateral GPi lesions are rare, apathy is common in Parkinson's Disease (Oguru et al., 2010; Pedersen et al., 2009a, 2009b; Starkstein, 2009; Starkstein et al., 2009), as well as in other neurodegenerative disorders, including Huntington's and Alzheimer's disease (Bonelli and Cummings, 2008; Chow et al., 2009; Marin, 1991; Starkstein et al., 2006). These conditions often involve disruption of cortico-striato-thalamo-cortical loops (Alexander et al., 1986) but the mechanisms underlying apathy when there is widespread neuro-degeneration has been difficult to study. Focal lesion cases such as KD provide important information about the neural substrates underlying apathy and modulation of this behavioural state with neuropharmacological intervention.

These investigations show that apathy following basal ganglia lesions is associated with indifference to reward that can be modulated by dopamine. I investigate the effects of dopaminergic modulation on oculomotor decisions in healthy volunteers in experiments reported in Chapters 5 and 6. Studies of Parkinson's disease patients as a model of apathy and/or impulsivity are further reported in Chapter 7.

# 5. The effects of levodopa on oculomotor decisions

# 5.1 Introduction

Though cognitive effects of dopaminergic modulation have been recognised experimentally (Cools et al., 2002; Dolan et al., 1995; Goldman-Rakic et al., 2004), cognitive effects have not been the usual therapeutic target of dopaminergic drugs in Parkinson's Disease (MacDonald and Monchi, 2011; MacDonald et al., 2011). In Parkinson's disease, levodopa is primarily used to treat the motor symptoms of the disorder, but cognitive and psychiatric effects are often reported (Choi et al., 2000; Molloy et al., 2006). Furthermore, levodopa has been implicated in development of impulse control disorders in Parkinson's patients (Weintraub et al., 2010; Grosset et al., 2011; Voon et al., 2011c, 2011d). This suggests that levodopa can modulate decision-making. That notion is supported by experiments which demonstrate changes in timing, probability and risk evaluation in healthy volunteers (Pessiglione et al., 2006; Pine et al., 2010; Pleger et al., 2009) and reward-based decision making in patients (Graef et al., 2010). The experiments described in this chapter investigate potential effects of L-dopa upon oculomotor decisions in young, healthy volunteers performing eye movement tasks.

## 5.1.1 The Cognitive Effects of Levodopa

### 5.1.1.1 L-dopa affects reaction time and time perception

A study measuring key press responses to a visual stimulus found shorter mean RTs in the L-dopa condition than placebo and also reduced variance in the responses (Rihet et al., 2002). There is evidence to suggest that the role of the basal ganglia in producing internal representations of time is dopaminergically mediated (Rammsayer, 1993). Dopaminergic mechanisms are thought to be involved in the regulation of the internal 'pacemaker' (Buhusi and Meck, 2002). Most time perception drug studies have used more D2 receptor selective dopamine agonists, however L-dopa (200mg) has been found to affect time interval estimation - lengthening estimates in the 'seconds' range [estimates required were 6 and 17 seconds] by 0.87s when averaged across target intervals and age groups - without changing reaction time (Rakitin et al., 2011).

### 5.1.1.2 L-dopa has oculomotor effects

There is only one reported study of the effects of L-dopa upon saccadic latencies in healthy volunteers. This experiment found fewer correct anti-saccades following L-dopa (100mg) administration, but no effects on reflexive saccades (Duka and Lupp, 1997). The authors noted that the L-dopa effect was directly opposed to the effect of incentive (monetary reward) on the task. The monetary reward increased accuracy. The same study also found no effect of L-dopa upon logical reasoning or on a rapid information-processing task.

With caution, we might seek further evidence from the patient literature: Electro-oculographic data demonstrated improved saccade *amplitudes* following a single dose of L-dopa (200mg) given to PD patients but significant changes in latency were not seen (Rascol et al., 1989). A more recent study has found that L-dopa (at patient's usual doses) slowed reactive saccades (pro-saccades) in a Parkinson's patient population (Michell et al., 2006) compared to baseline measurements 'off drug'. However, this effect was not uniformly present in all patients, and the group effect appears to have been driven by a few, large, individual responses. Another group

replicated this finding however, and also found that L-dopa (at the patient's usual doses) improved the accuracy (reduced the error rate) of voluntary anti-saccades (Hood et al., 2007).

#### 5.1.1.3 Effects upon decisions and reward processing

The important experimental influence of dopaminergic modulation upon reward learning and behaviour in humans, non-human primates and smaller animals is well described (Robbins and Everitt, 1996). More recent human experiments using behavioural tasks and fMRI have begun to reveal the extent of L-dopa's wide-ranging effects. These include "bottom-up" effects upon low-level somatosensory decisions (Pleger et al., 2009). L-dopa enhanced the effects of higher anticipated reward, which then improved tactile decisions. This was in contrast to Haloperidol (a DA antagonist) that impaired the same task performance. The reward and DA effects were found to correlate with changes in striatal and orbitofrontal BOLD signal.

More cognitively complex "top-down" effects are also recognised. In a study that compared the effects of L-dopa and haloperidol, a DA antagonist (Pessiglione et al., 2006), L-dopa was associated with more frequent choice of a high-probability gain option compared to haloperidol. There was no effect on the frequency of choosing a low probability loss. This meant that L-dopa treated subjects won more money in the task overall than those taking haloperidol. This drug-induced behavioural difference was correlated with changes in BOLD response of opposing direction in the striatum, suggesting an anatomical substrate for the heightened reward sensitivity induced by L-dopa. Such heightened reward sensitivity may combine with impaired temporal evaluation and lead to heightened temporal discounting (Pine et al., 2010). Temporal discounting is often used as an index of impulsivity (Wittmann and Paulus, 2008). Impulsivity may be associated with impaired risk evaluation (Horvath and Zuckerman, 1993; Kreek et al., 2005). However, another study found no effect of L-dopa upon subjects' evaluation of risk, and its authors therefore propose that the main dopaminergic effect upon decision making is through modulation of response to reward (Symmonds et al., 2013). A recent study shows that L-dopa appears to degrade discrimination of salient loss outcomes (which should lead to reversals in a set switching task) in PD patients (Shiner et al., 2014). This degradation is associated with reversal in the expected activity in ventromedial prefrontal cortex (vmPFC). This is consistent with patients' poor learning from punishment in reward tasks (i.e. failure to learn from mistakes).

### 5.1.2 Experimental design

We decided to investigate the effects of dopaminergic modulation in healthy volunteer subjects - both under the influence of L-dopa and without. In order to do this, we designed a randomised, double blind, counter-balanced, within-subject crossover design to compare the effects of L-dopa with placebo on both measures described in previous chapters.

It was hypothesised that L-dopa would have effects upon reward sensitivity, heightening it and thereby causing shorter latency responses in the lateral reward task (Chapter 3). This might also lead to greater anticipatory behaviour in the traffic light task (Chapter 2), though perhaps at the expense of more errors. To control for saccadic reaction time (SRT) effects in our tasks, we included the saccadic reaction time (SRT) task (Chapter 2). In order to extract risk avoidance we

also used the reverse traffic light task (Chapter 3), which is not dependent upon reaction time effects. In order to compare our experimental subjects with previously tested controls, we administered both the BIS-11 and TPQ (Chapter 3). Choice of dose and the details of the experimental design are discussed in the methods section.

We wished to extract the effect of the drug compared to placebo independently from influences of learning due to training. For this reason we included a training session prior to drug/placebo sessions, an additional control measure which frequently absent from many drug intervention studies. We hoped that this would serve to eliminate major training effects and allow us to focus upon effects genuinely attributable to the drug while remaining cognisant of the possibility of an interaction between the effects of the drug and learning.

A randomised, counterbalanced design was used so that, following training, 50% of subjects were randomised to a 'placebo first' group and the remaining 50% to a 'drug first group'.

#### 5.1.2.1 Pharmacology

L-dopa (L-3,4-dihydroxyphenylalanine, levodopa) is synthesized from the amino acid L-tyrosine in the body and brain. L-dopa is the precursor to the catecholamine neurotransmitters dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline). It is peripherally decarboxylated into inactive metabolites. To prevent this, the drug is given with a dopa decarboxylase inhibitor, which does not cross the blood brain barrier, thus allowing the drug to have effects on the organ intended. Plasma concentration peak is reached quickly (<60 minutes in the fasted state (Contin and Martinelli, 2010)) and levels remain high between one and 3 hours post-dose (Crevoisier et al., 1987). A previous eye movement study found significant effects of L-dopa 1 hour post administration were no longer present 5 hours post administration (Duka and Lupp, 1997). We therefore chose to commence testing an hour after drug ingestion. Testing was complete within two hours.

#### 5.1.2.2 General levodopa effects & dose rationale

A large dose of L-dopa (200mg + 50mg benserazide) has been found to cause sedation in drug-naive, healthy volunteers (Andreu et al., 1999). L-dopa induced sedation scores have found to correlate (positively) with reaction time in a button-press task (Micallef-Roll et al., 2001). Due to the risk of side effects (especially nausea) at this dose, these studies used pre-administration of domperidone. We wished to avoid nausea, sedation and reaction time effects and therefore chose to use Madopar tablets containing 100mg of L-dopa in combination with 25mg benserazide, a dopa decarboxylase inhibitor. This is also a dose that might be used on initiation of therapy in a Parkinsonian patient (Holloway et al., 2004). Previous studies using this dose were successful in generating cognitive changes without resulting in significant side effects (Duka and Lupp, 1997; Pessiglione et al., 2006).

## 5.2 Methods

20 right-handed healthy volunteers were recruited of whom 12 (6 female, mean age 22.6yrs, SD 3.4) went on to complete the study. (The remaining 8 chose not to proceed beyond the training session. Their results are not included here but are presented in Chapter 2 upon age effects and Chapter 3 on task variants).

Each subject was randomly assigned to receive drug or placebo in the second session and the opposite (placebo or drug) in the third. Pre-randomisation was achieved by ensuring that a set of letter-coded envelopes contained an equal number of 'drug-first' and 'placebo-first' options. The experimenter was kept unaware of the order until the study and analysis were complete. Subjects were also blinded, as the drug and placebo preparations were not easily distinguished and had no identifying markings. At the end of the study, there were an equal number of subjects in the 'drug-first' and 'placebo-first' groups.

Subjects were asked to fast for four hours prior to their testing session to ensure an empty stomach, therefore increasing the speed to reach peak plasma L-dopa concentration. Sessions were conducted at a prearranged time. This time was kept as the start of testing for drug and placebo sessions, which were held at one and two weeks after training, to reduce the influence of diurnal variation in performance. At the training session, subjects were asked to choose from a set of envelopes, and this determined the order of the drug and placebo conditions for the remaining 2 sessions.

When subjects arrived for the second session, they were given either Madopar dispersible 125mg (L-dopa 100mg + benserazide 25mg) or a dispersible multivitamin in liquid. Neither tablet imparted any distinctive flavour or colour which would have unblinded the participant or experimenter.

The following tests and tasks were administered during the 2-hour period:

### 5.2.1 Questionnaires

During the training session, subjects completed two questionnaires before and/or during breaks between eye movement testing:

1) The Barratt Impulsiveness Scale (BIS-11). This is a measure that has been used in multiple studies of impulsivity in both health and disease (see Chapters 2 & 3 for further discussion).

2) The Cloninger Tridimensional Personality Questionnaire (TPQ, (Cloninger, 1987) (Chapter 3). It was hypothesised that there might be an inverse correlation between the Novelty-Seeking (NS) dimension and risk avoidance in our tasks, a positive relationship between the Harm Avoidance (HA) dimension and task risk avoidance and a positive correlation between the Reward Dependence (RD) dimension performance on our rewarded tasks.

### 5.2.2 Eye Movement Tasks

Following drug/placebo administration in sessions 2 and 3, subjects were asked to wait in the lab for an hour before testing commenced. This was to ensure that drug plasma levels reached their peak as testing began. Subjects were free to read, work or use the internet during this period but were continuously monitored for any side effects. They were also asked not to drink any caffeine prior to or during this first hour, but were offered as much fluid as they wished.

#### 5.2.2.1 SRT Task

The SRT Task (See Chapter 2, Figure 2.2) required subjects to make eye movements *as fast as possible* when a red STOP signal changed to a green GO signal. The delay from red to green on each trial varied randomly between 500 and 1000ms (rectangular distribution). This task was not rewarded. The saccades required alternated between a rightward saccade (odd numbered trials, from -10 to +10 degrees), and a leftward saccade (even numbered trials, +10 to -10 degrees). Confirmation of a completed saccade was acknowledged by an auditory "ping" and by the cruciform target changing from white to red. Erroneous, early saccades caused an aversive "beep" and the trial to repeat.

#### 5.2.2.2 The Traffic Light Task

In the Traffic Light Task (Chapter 2, Figure 2.1), subjects were asked to make as much money as possible by making saccades *as quickly as possible* in response to a traffic light stimulus. Each trial begins with a red light that, after 1000ms, turns amber. The amber duration varies randomly from trial to trial but is drawn from a normal distribution (mean 750ms, SD 125ms). Following the amber light, a green GO signal appears. Subjects then made a saccade from the stimulus to a cruciform target at 20 degrees retinal eccentricity. Trials alternated between left to right (odd numbered trials) and right to left (even numbered trials). Correct saccades were rewarded with either a "ping" for latencies of >=200ms or a "Kerching" for latencies of <200ms. Reward was displayed at the target location for each trial and a cumulative total was displayed immediately below the target.

The reward ($R$) for a successful saccade was calculated by an exponentially decaying discounting function in the form:

$$R = ae^{-\left(\frac{t-t_0}{k_1}\right)}$$

Where $a$ = 150, $k_1$=100 and $t$ represents the saccade onset time relative to green onset ($t_0$, milliseconds).

Erroneously early saccades, before the GO signal were punished by an aversive "bleep" and a fixed negative reward of -10 pence.

Studies in similarly aged healthy volunteers had already demonstrated that this task elicited a bimodal distribution of saccadic responses (See Chapter 2). We were interested in the effects of L-dopa upon the distribution of 'reactive' and 'anticipatory' saccades.

#### 5.2.2.3 Reverse Traffic Light Task

The *forward* traffic light task tests multiple subject variables, including reaction time, reward sensitivity and risk aversion. The reverse traffic light task (Chapter 3, Figure 3.3) was developed in order to look at risk avoidance, independent of reaction time. In this task, subjects were asked to accrue as much as reward as possible. To do this, they had to fixate a traffic light stimulus, which was green at the start of each trial. After 1000ms it turned amber. The amber duration was randomly chosen on each trial from a normal distribution (mean 1500ms, SD 250ms). [This was deliberately different from the *forward* traffic light task, to avoid learning effects causing an interaction between the two tasks. The task was also presented before and after the forward traffic light task to minimise interaction effects].

After the amber light, a red STOP signal would appear. If subjects made no saccade prior to red onset, they received a fixed -10 pence penalty and heard an aversive "bleep". The aim was to wait *as long as possible*. The later in the amber light subjects made their saccade, the greater the reward they received. In other words, subjects were trying to anticipate the red light but ensure that they responded before it appeared – similar to "playing chicken".

Successful anticipation of the red light was rewarded in a similar fashion to the forward task except that the reward *increased* exponentially as the red light onset approached. The reward calculation was necessarily slightly more complicated in this task, as the distribution had to be 'fitted' into a variable amber light duration. This ensured that the reward was always a maximum of 150 pence but meant that reward varied both as a function of the anticipatory interval and the length of the amber light on each trial.

$$R = Ae^{(ts-t\alpha-t\Omega)/t\Omega \bullet \kappa}$$

*R=reward (in pence), A=150, $t_s$ = time of saccade, $t_a$ = time of amber onset, $t_o$ = time of red light onset, $\kappa$=0.1*

#### 5.2.2.4 Lateral Reward Task

The lateral reward task (Chapter 3, Figure 3.1) was adapted from a task designed to look at reward sensitivity in non-human primates (Hong and Hikosaka, 2008). We used our version of this task to investigate effects of L-dopa versus placebo in affecting reward sensitivity. In this task, subjects were asked to attend a central white fixation spot. After 1000ms, the fixation disappeared and an identical target appeared at either -10 or +10 degrees retinal eccentricity (this varied randomly from trial to trial, 50% of targets were leftward and 50% were rightward). To begin with, either leftward *or* rightward targets were rewarded according to saccade latency. Reward was presented numerically with a pound coin symbol at the target location and subjects heard an auditory reward similar to that in the traffic light task ("ping " SRT>=200ms,

"Kerching!" for SRT<200ms). Saccades to targets on the non-rewarded side were acknowledged with a change in colour of the target (white to red) and a non-rewarding "bleep". After a jittered number of trials, the rewarded side would switch. On average, 60 leftward trials were presented and 60 rightward. On average, 30 each of these would have been rewarded target locations. The reward side 'switch' occurred approximately every 20 trials (5 switches per 120 trials).

The following experimental protocol was followed:

| | |
|---|---|
| Time (t) = 0 minutes | |
| | Written consent & Drug (Madopar 125mg) / Placebo (Multivitamin tablet) Ingestion |
| | Subjects were weighed |
| t = 60 | SRT task (100 trials) |
| | Lateral Reward task (120 trials) |
| | Reverse traffic Light Task (100 trials) |
| | Traffic Light Task (10 blocks x 50 trials) |
| | Lateral Reward task (120 trials) |
| | Reverse traffic Light Task (100 trials) |
| t = 120 | Testing complete, feedback to subjects, debrief and reward payment |

During the training session, subjects completed the BIS-11 and the TPQ before proceeding immediately with the eye movement tasks.

The reverse, lateral reward task and SRT task were developed during the initiation of the study. Therefore the number of subjects participating in each task varied slightly as follows:

| **Session** | **Session 1** | **Session 2** | **Session 3** |
|---|---|---|---|
| **SRT Task** | 9 | 12 | 12 |
| **Traffic Lights** | 12 | 12 | 12 |
| **Reverse Task** | 11 (1 block only) | 12 | 12 |
| **Lateral Reward** | - | 8 | 8 |

## 5.3 Results

Subjects complained of no side effects, or overt mood change in response to L-dopa. There were no drug-related complaints or adverse events.

### 5.3.1 Questionnaires

The subjects' mean BIS-11 scores were all within the normal range (mean 60.2, SD 11.3). Both the mean and variance were similar to those found in our student survey (see Chapter 3) and in a previous study in Baylor undergraduates authored by the scale's inventor (Patton et al., 1995).

The TPQ results for novelty seeking (mean 16.7, SD 4.9) correlated well with the BIS-11 totals, with an $R^2$ of 0.699 ($p<0.0005$). The means and variances of scores in each category were consistent with normal ranges from previous studies (e.g. (Otter et al., 1995)).

We hypothesised that subjects who scored more highly on the impulsiveness and novelty seeking scales would behave more aggressively in our rewarded tasks, taking greater risk in order to accrue greater rewards.

### 5.3.2 Saccadic reaction Time (SRT) Task

The saccadic reaction time task was developed and introduced after the initiation of this study. Therefore only 9 of the 12 subjects were tested on this task in the first (training) session. The mean SRT for these subjects was 331ms. In Sessions 2 & 3, all 12 participants completed the SRT task at the beginning of the testing session. In Session 2, the mean SRT was 324ms. A paired Student T-test comparing mean latencies in the first and second sessions showed no statistically significant difference. In session 3, the mean was reduced at 305ms. This was significantly faster than Session 2 (Paired, 2-tailed, Student T-test, $t(11)=2.52$, $p<0.03$). There was therefore a practice effect across sessions 2 and 3 (Figure 5.1). The lack of significant effect between sessions 1 and 2 may be due to the reduced sample size (only 9 of 12 subjects completed this task in session 1).

We hypothesised that L-dopa would slow simple saccades, as previously demonstrated (Hood et al., 2007; Michell et al., 2006). There was a non-significant slowing effect of L-dopa ($SRT_D$) compared to placebo ($SRT_P$) (322ms vs 308ms, Paired, 1-tailed, Student T-test, $t(11)=-1.65$, $p=0.06$) (Figure 5.1).

We anticipated a training effect would also shorten latencies. In the placebo condition, SRTs were non-significantly shorter than in training ($SRT_P$=308ms vs $SRT_T$=330ms; 1-tailed, Student T-test, $t(22)=-1.09$, $p=0.14$). In the drug condition ($SRT_D$=322ms), responses were also non-significantly faster than in training ($SRT_T$=330ms).

To investigate whether there was an interaction between the drug/placebo condition and session order, a two-factor ANOVA with replication was performed (Figure 5.2). This demonstrated a non-significant interaction between the drug condition and session ($F(1,23)=3.38$, $p=0.08$) suggesting a possible dopaminergic influence on learning. Saccadic

latencies were non-significantly slower for subjects given drug first ($SRT_{P1}$=302ms vs $SRT_{D1}$=346ms; 2-tailed, Student T-test, t(10)=1.72, p=0.12), whereas they were non-significantly faster for those given drug compared to those given placebo in the second session ($SRT_{P2}$=313ms vs $SRT_{D1}$=297ms; 2-tailed, Student T-test, t(10)=-0.79, p=0.45).

Plots of the saccade distributions from this task revealed a typical recinormal distribution of latencies (Figure 5.1). These were well modelled by a single LATER unit for which mean and variance of the rates of rise were estimated using maximum likelihood estimation (Figure 5.3). The modelled medians for each individual closely resemble the true medians of the data and correlate significantly (Table 5.1 & Figure 5.4). Maximum likelihood estimation was used to find parameters of best fit for recinormal distributions to describe the data. Modelling the group data found medians, which approximated well to the data (see Fig 5.4).

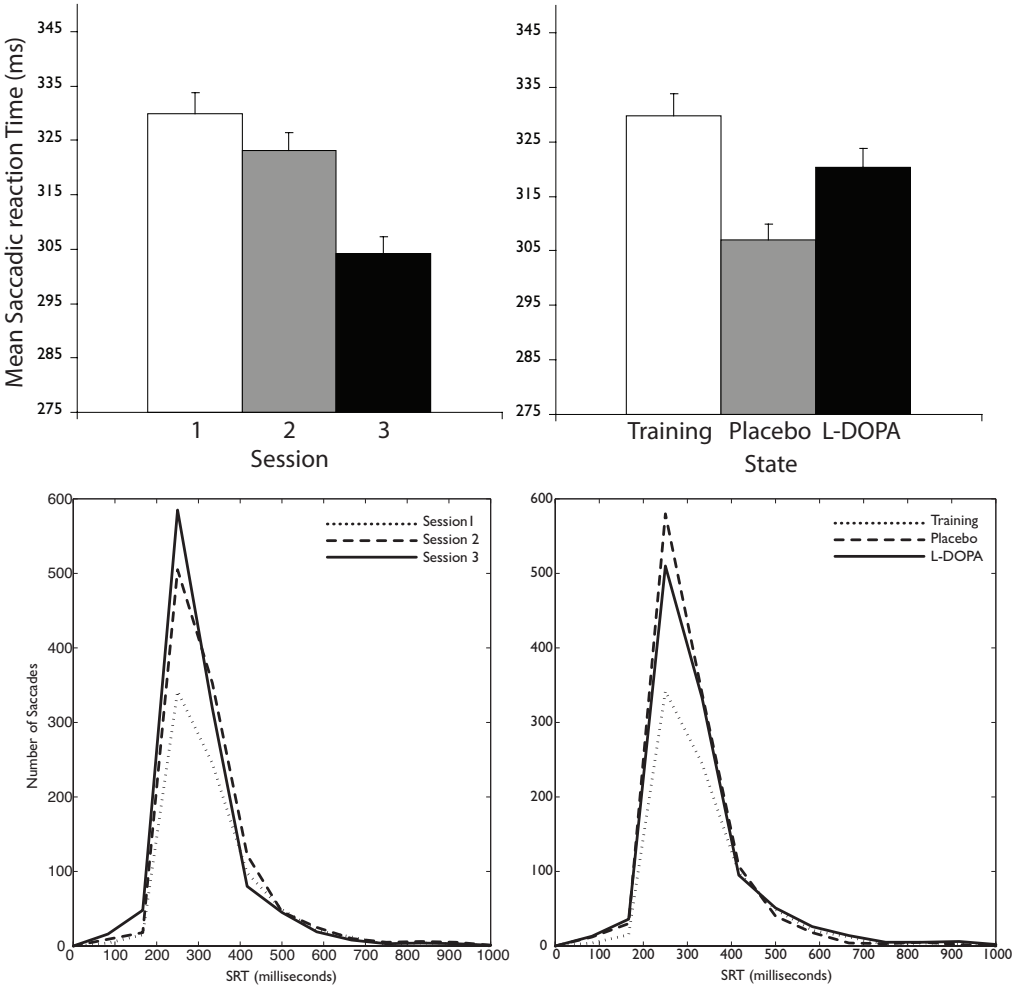



**Figure 5.1 The SRT Task: Effects of Training and Drug**

Training improved reaction times non-significantly between sessions 2 and 3. L-dopa non-significantly slowed SRT compared to placebo.

Top panels: histograms demonstrate mean SRT for the whole group by session (top left) and state (top right). Lower panels: saccadic distributions (for the whole group) by session (bottom left) and state (bottom right).

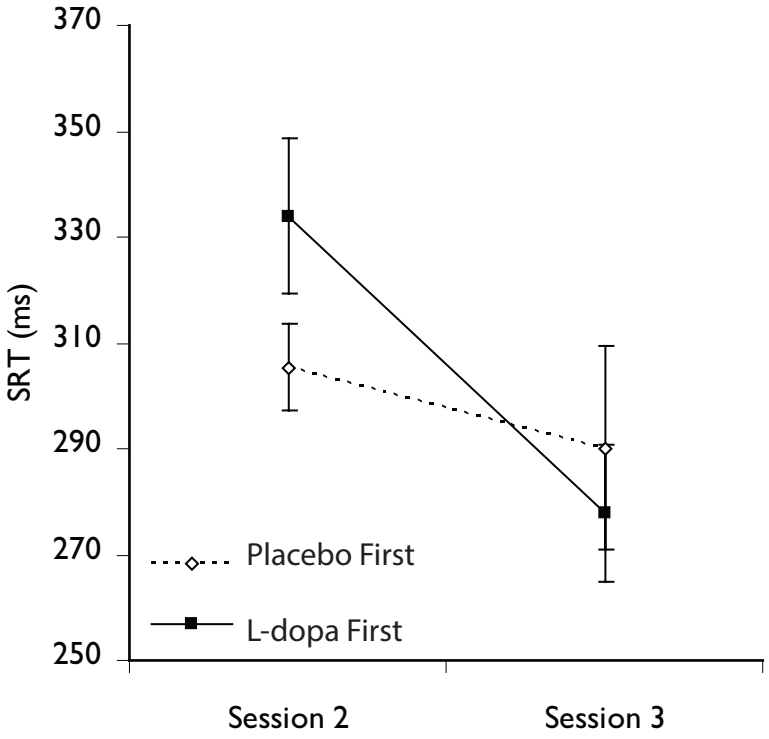



**Figure 5.2 SRT Task: The effect of session order**

Subjects who took drug first were slower in the first of the two sessions. In the second session, the mean SRT of those taking drug was, in contrast, reduced. This difference led to a non-significant interaction between session and drug/placebo order ($F(1,23)=3.38$, $p=0.08$).

| Session | Mean (ms) | SD (ms) | Median | Modelled Median | Correlation Coefficient (Pearson's r) | Significance Level |
|---|---|---|---|---|---|---|
| **1 (n=9)** | 331 | 112 | 305 | 307 | 0.95 | p<0.001 |
| **2 (n=12)** | 324 | 109 | 301 | 304 | 0.97 | p<0.001 |
| **3 (n=12)** | 305 | 101 | 287 | 294 | 0.93 | p<0.001 |

| State | Mean (ms) | SD (ms) | Median | Modelled Median | Correlation Coefficient (Pearson's r) | Significance Level |
|---|---|---|---|---|---|---|
| **Training (n=9)** | 331 | 112 | 305 | 307 | 0.95 | p<0.001 |
| **Placebo (n=12)** | 308 | 93.2 | 289 | 294 | 0.99 | p<0.001 |
| **Drug (n=12)** | 322 | 117 | 299 | 305 | 0.94 | p<0.001 |

## Table 5.1 Modelling Data from the SRT Task

Parameters of best fit for a single LATER unit derived from maximum likelihood estimation (MLE) compared and correlated with subjects' reaction time data.

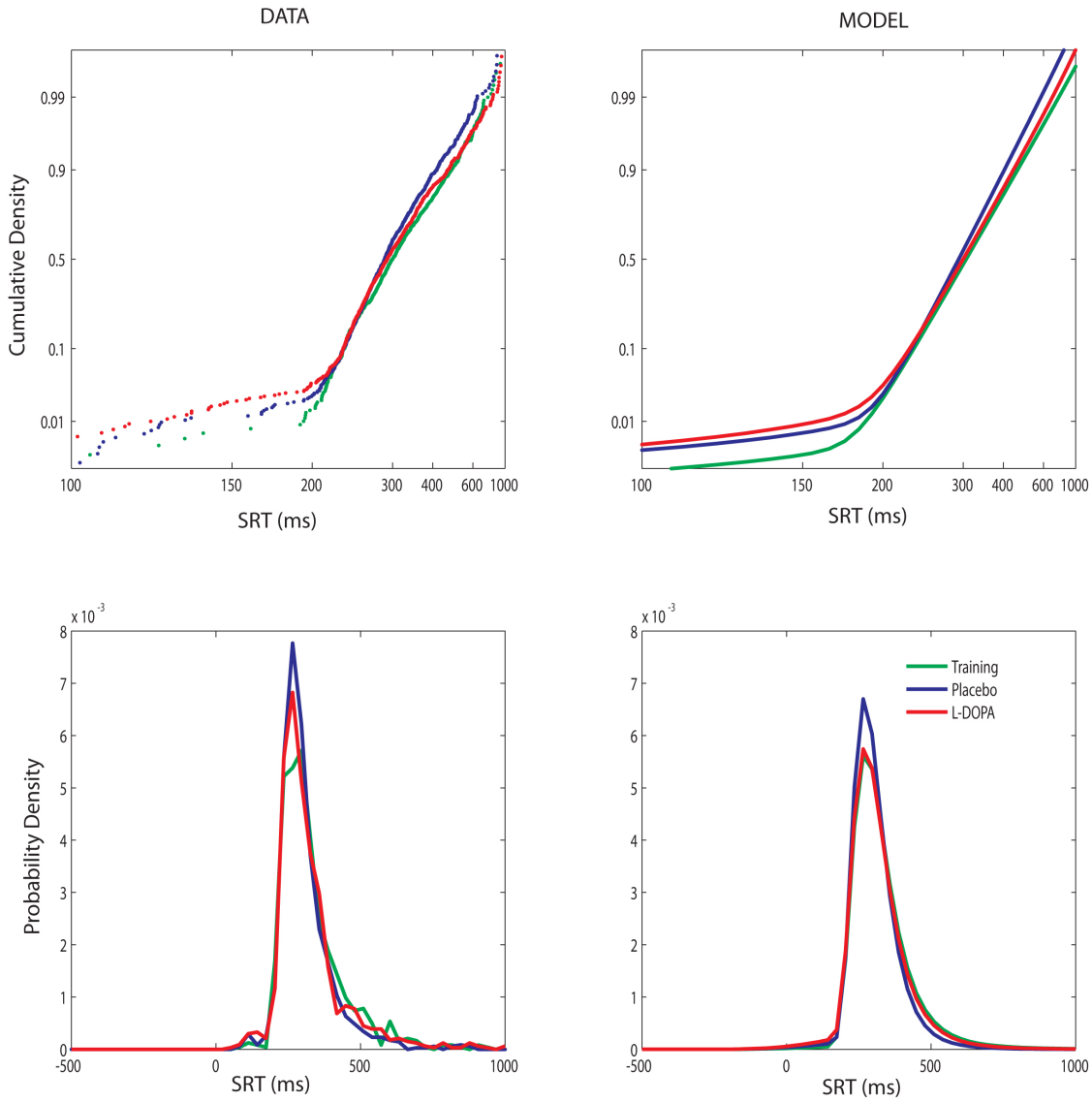
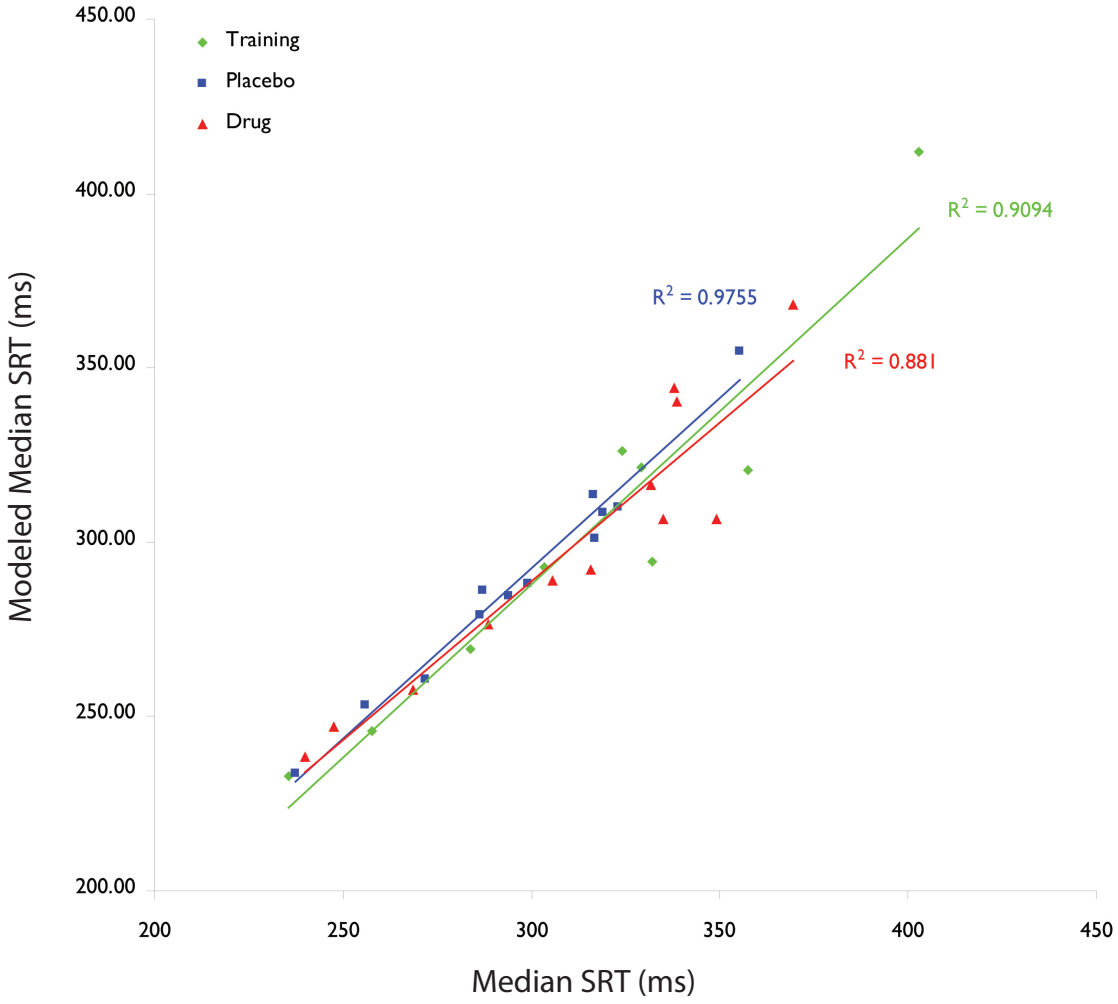



**Figure 5.3 SRT task responses are well modelled by a single LATER unit**

The raw data is represented in the left hand panels for training, placebo and L-dopa conditions. The derived, modelled data for each condition is shown in the right hand panels. The upper panels show cumulative density distributions of saccadic latencies whereas the lower panels show the same data plotted as probability density distributions. The rendering of the positively skewed quasi-normal saccadic response latency probability density function into a linear cumulative density function is the basis for the LATER model (see Chapters 1&2).




*All correlations are statistically significant (p<0.001)*

**Figure 5.4 Correlations between SRT Task data derived true median latencies and those found by maximum likelihood estimation of parameters for a LATER unit**

### 5.3.3 Traffic Lights

#### 5.3.3.1 Training Effects

The twelve subjects all completed 3 sessions of 500 trials of the Traffic Light task. Across the three sessions, performance (measured as reward obtained) significantly improved on each occasion, as we hypothesised. In the first session, mean reward was 14.9p per trial, in the second it increased to 21.3p (paired, 1-tailed Student t-test, $t(11)=-3.68$, $p=0.002$). Reward significantly rose again in the third session, to 24p (paired, 1-tailed Student t-test, $t(11)=-3.29$, $p=0.004$).

This was due to both increased anticipation across all 3 sessions (Figure 5.5) which is indicative of a better strategy. In Session 1 there was a mean of 44 correct anticipations (responses between 0 and 200ms) verses mean 133 correct anticipations in Session 2 (paired, 1-tailed Student t-test, $t(11)=-10.20$, $p<0.0001$). The anticipations increased significantly again in Session 3 (165 anticipations versus 133, paired, 1-tailed Student t-test, $t(11)=-2.97$, $p=0.006$).

The improved reward occurred despite significantly increased errors in the second and third sessions compared to the first (Figure 5.5). Mean Error1 = 59.6, Mean Error 2 = 108.8; (paired, 1-tailed Student t-test, $t(11)=-4.76$, $p<0.001$); Mean Error 3 = 107.8 (paired, 1-tailed Student t-test, $t(11)=-4.25$, $p<0.001$).

This training effect is visible from the raw saccadic data distributions (Figure 5.6). In the first session, there was only modest anticipatory behaviour (though a separate anticipatory distribution is still apparent). Following the initial major increase in anticipatory responding (from sessions 1 to 2), there is a smaller increase in the height of the anticipatory peak from sessions 2 to 3, but this is insufficient to cause a significant increase in the numbers of saccades recorded with latencies of <200ms.

#### 5.3.3.2 Drug Effects

Analysis of variance was performed to compare the influence of session effects and drug/placebo condition upon the three variables: reward, anticipations and errors (fig 5.7). There was no interaction between session and drug/placebo when considering reward. However, there was a trend toward an interaction when considering the number of anticipations ($F(1,23) = 3.68$, $p=0.07$). There was a significant interaction between session and drug/placebo condition when considering the number of errors ($F(1,23) = 5.60$, $p=0.03$). Considering each group separately, the 'drug first' group (mean 18.9%, SD 8.7%) made non-significantly fewer errors in the second session than did those receiving placebo (24.6%, SD 6.2%). In the third session, the situation was reversed, with those receiving L-dopa (the 'placebo first group') now making non-significantly more errors (mean 25.2, SD 5.9% versus 18.0, SD 5.3%, Figure 5.8). This raises the possibility of a speed/accuracy trade off when subjects are administered L-dopa – the first group favouring slower more accurate responses, the second group choosing faster but more error-prone performance.

When both sessions are combined, there are no significant differences in any of the three measures between drug and placebo; however, there was a small (non-significant) decrease in reward with L-dopa due to an increase in the error rate. There is a trend toward more errors with L-dopa (24.8%) versus placebo (21.4%) but this does not reach significance. There was no change in correct anticipations (Figure 5.8). Therefore, following the major improvement after a single training session, performance remained static despite both further training and drug administration (Figure 5.9).

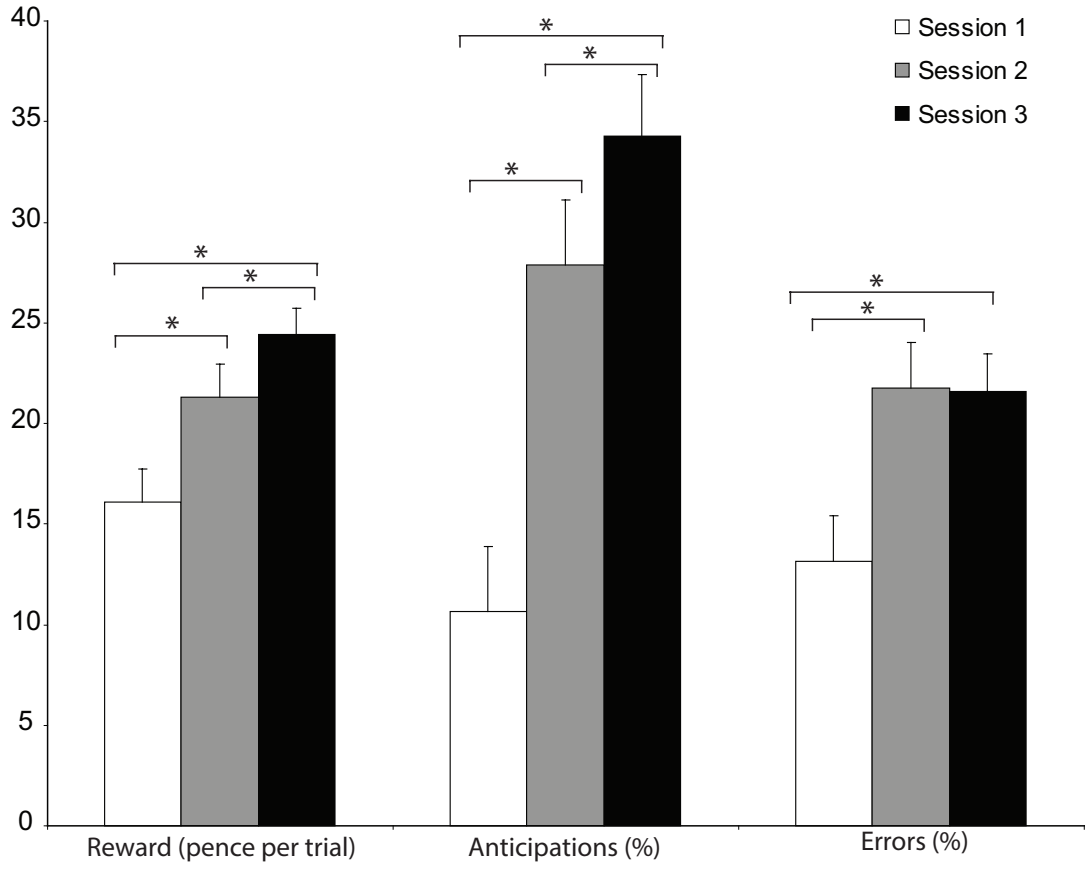



**Figure 5.5 Traffic Light Task Training Effects**

Subjects significantly increased their anticipatory responding across the three sessions and significantly increased their error rate, which subsequently plateaus as they find the optimal balance between caution and anticipation. This optimisation leads to significant increased in reward between each session.

**Statistically significant difference*

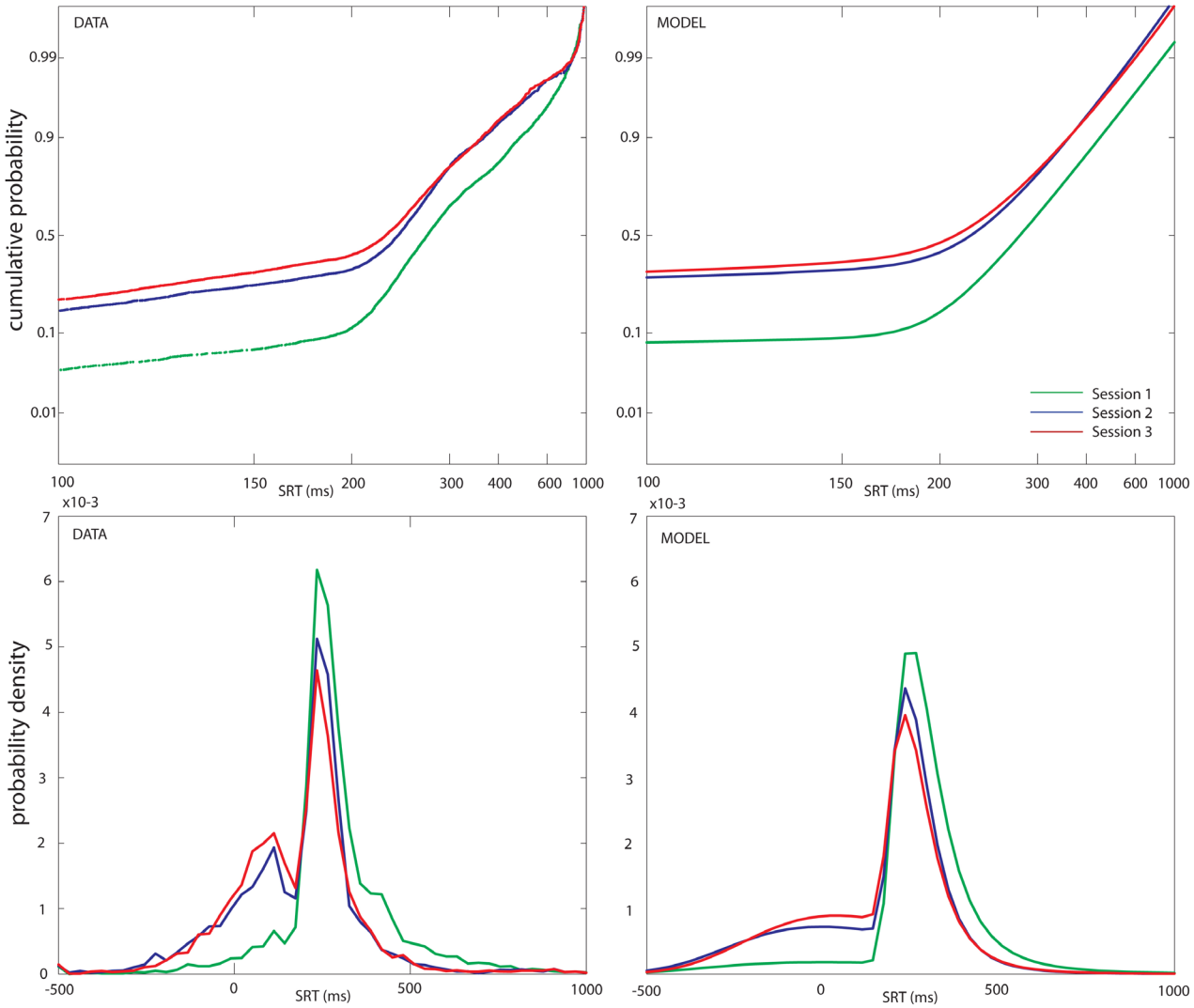



**Figure 5.6 Training Effects upon Traffic Light Task Saccade Distributions**

Between sessions 1 and 2, the major change is an increased anticipatory distribution. This further enlarges in the 3rd session. The reactive distribution remains quite constant throughout.

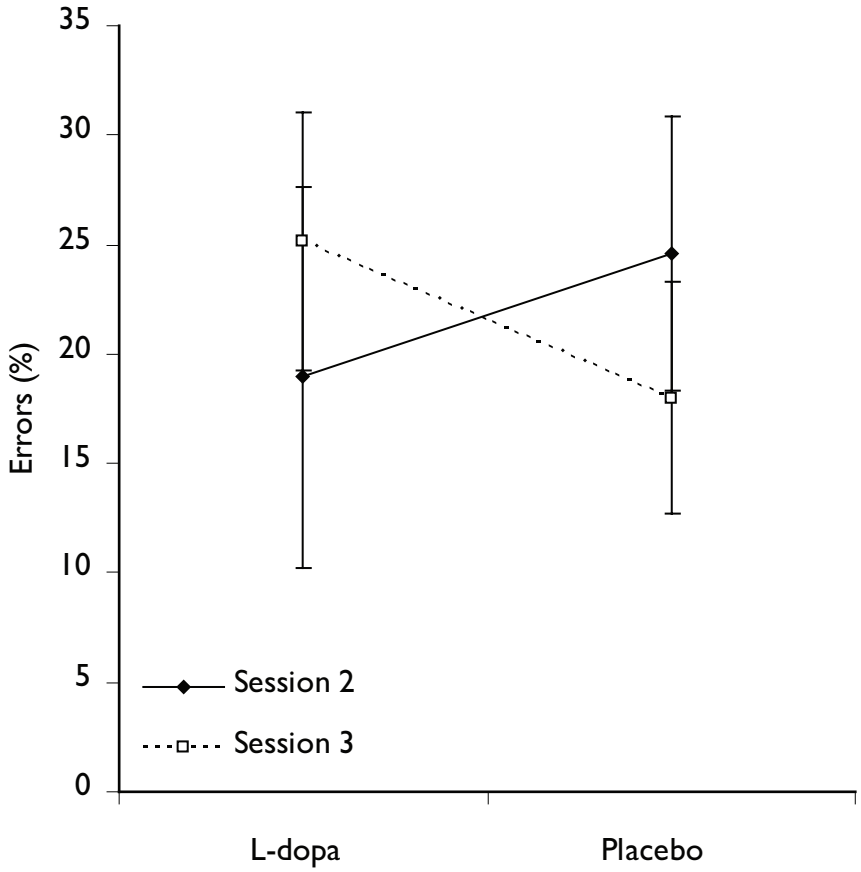
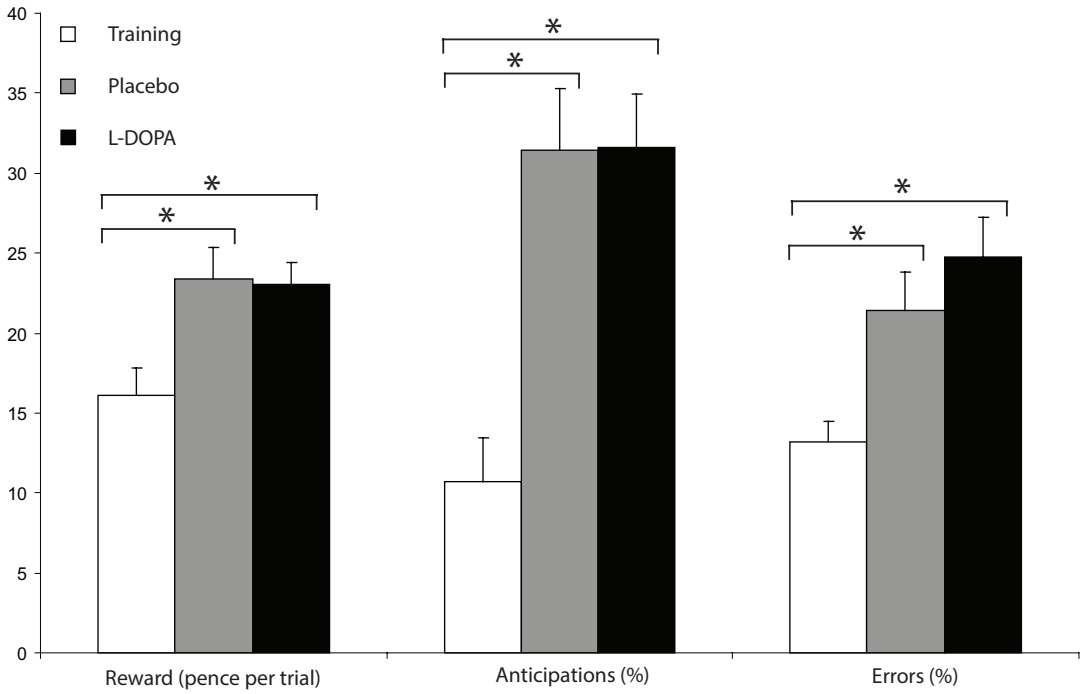



**Figure 5.7 The interaction between session effects and drug/placebo condition upon error rates in the Traffic Light Task**

Subjects receiving L-dopa in the second session made non-significantly fewer errors than those receiving placebo. In the third session, the reverse was true, with L-dopa recipients making a non-significantly increased number of errors.




**Statistically significant difference*

**Figure 5.8 Drug Effects on Traffic Light Task Performance**

There is a marked and significant improvement following the training session, but no significant differences between performances on drug versus placebo.

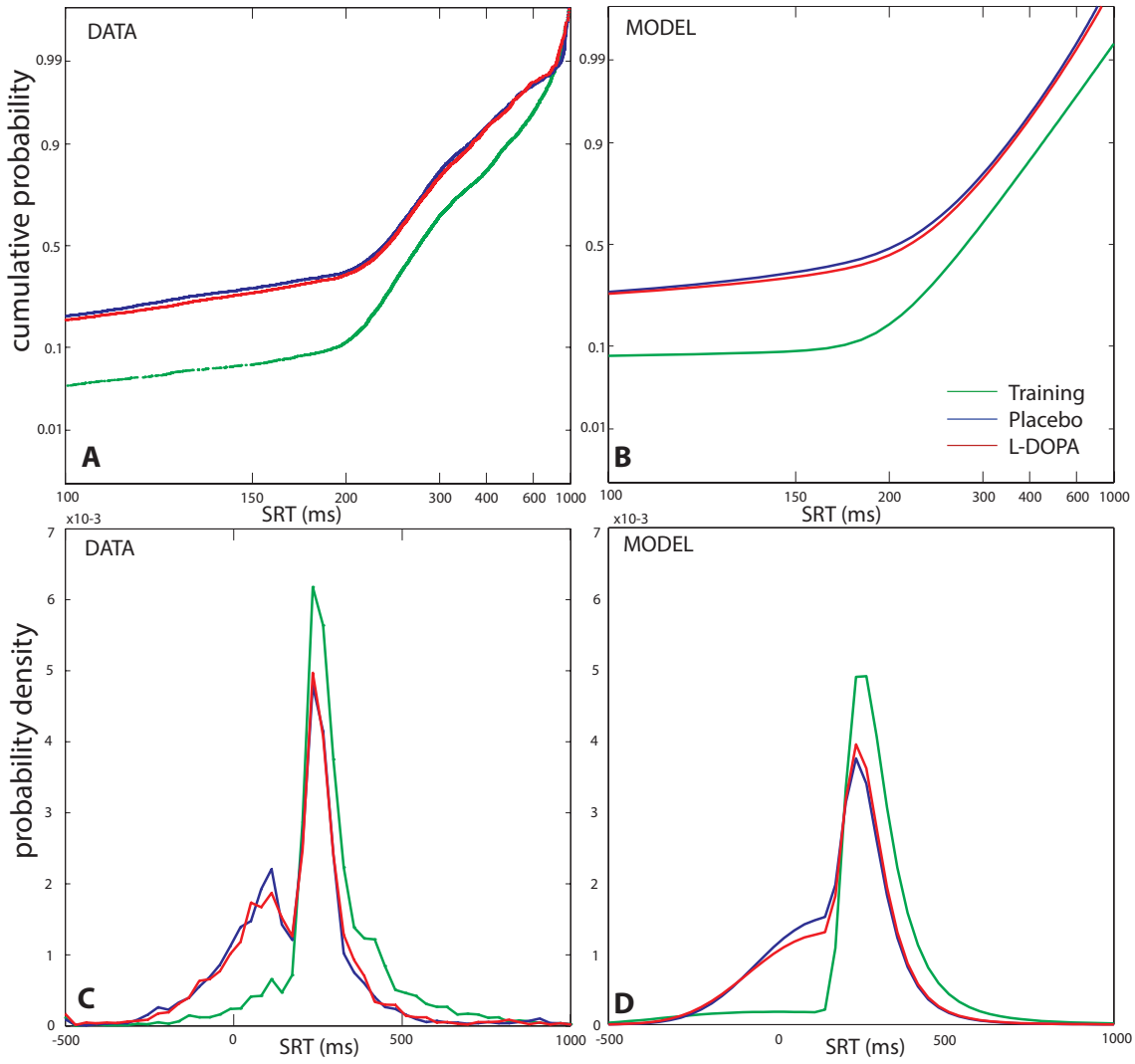



**Figure 5.9 Drug Effects Upon Traffic Light Task Saccade Distributions**

There is a visible difference between the training session, which shows little anticipation, and the two experimental sessions. However, responses in the drug and placebo sessions are very similar.

Modelling using MLE to find parameters of best fit for a combination of two LATER units fits the data well.

**A** Cumulative probability function for saccadic latency (raw data)
**B** Cumulative probability function for saccadic latency (modelled fit)
**C** Probability density function for saccadic latency (raw data)
**D** Probability density function for saccadic latency (modelled fit)

#### 5.3.3.3 Modelling the distributions

Maximum likelihood estimation was used to find parameters for two LATER units that fitted the Traffic Light Task response distributions well (Figure 5.9 and Table 2). Statistical analysis (not shown) of the anticipatory parameters revealed no significant differences between drug and placebo, but replicated the training effects found by analysis of the raw data.

| Session | Group Modelled Anticipatory Median (SD) | Mean Modelled Anticipatory Median (SD) | Group Modelled Reactive Median (SD) | Mean Modelled Reactive Median (SD) |
|---|---|---|---|---|
| **1** | 2277 (46.5) | 1758 (60.0) | 294 (32.9) | 303 (38.4) |
| **2** | 1034 (53.7) | 1078 (58.0) | 284 (32.5) | 295 (36.9) |
| **3** | 960.0 (66.8) | 1084 (65.6) | 305 (31.0) | 319 (34.3) |
| **State** | **Group Modelled Anticipatory Median (SD)** | **Mean Modelled Anticipatory Median (SD)** | **Group Modelled Reactive Median (SD)** | **Mean Modelled Reactive Median (SD)** |
| **T** | 2277 (46.5) | 1758 (60.0) | 294 (32.9) | 303 (38.4) |
| **P** | 1125 (41.2) | 1166 (65.5) | 272 (31.7) | 293 (31.8) |
| **D** | 1169 (40.8) | 1163 (58.1) | 273 (31.7) | 288 (32.0) |

### Table 5.2 Traffic Light Task Parameters

Parameters of best fit for the two distributions, anticipatory and reactive for sessions 1-3 and for Training (T), Placebo (P) and Drug (D). Anticipatory medians are with respect to amber onset. Reactive medians are with respect to green onset. All values are in milliseconds.

### 5.3.4 Reverse Traffic Lights

The reverse task was also added to the experimental protocol, as a measure of risk seeking/avoidance. 11 of the 12 subjects were trained prior to drug/placebo administration. During the training session, the 11 subjects completed one block of 100 trials. During the drug/placebo sessions, all 12 subjects completed two blocks of 100 trials.

There was a main effect of training, as hypothesised, with subjects improving their strategy (taking higher risk and incurring more errors) with each session, and thereby accruing more reward overall. The amount by which the subjects anticipated the end of the amber light decreased across the sessions (i.e. they were prepared to take greater risk in exchange for higher rewards). In the first session, their mean STOP anticipation interval (SAI, the amount of time *before* the red light that the saccade was made) was 378ms. This decreased significantly to 232ms in the second session (1-tailed Student T-test, $t(21)=2.90$, $p=0.004$) and was significantly reduced again to 214ms in the final session, respectively (paired, 1-tailed Student T-test, $t(11)=1.79$, $p=0.05$) Figure 5.10 & 5.11).

Analysis of variance of mean reward demonstrated no interaction of drug/placebo condition with session number (two factor ANOVA with replication, $p=0.94$). A similar analysis of the error rate showed a trend toward an interaction that was also not significant at the 5% level. Neither was there a significant interaction between session and anticipation of the STOP signal.

There was no significant difference between drug and placebo conditions. There was a trend toward a reduced mean anticipatory interval on L-dopa (214ms) versus placebo (232ms) but this did not reach significance. There was no main effect of drug on either reward or error rate. STOP anticipation showed a non-significant trend toward riskier behaviour under L-dopa (mean 214ms versus placebo mean 232ms).

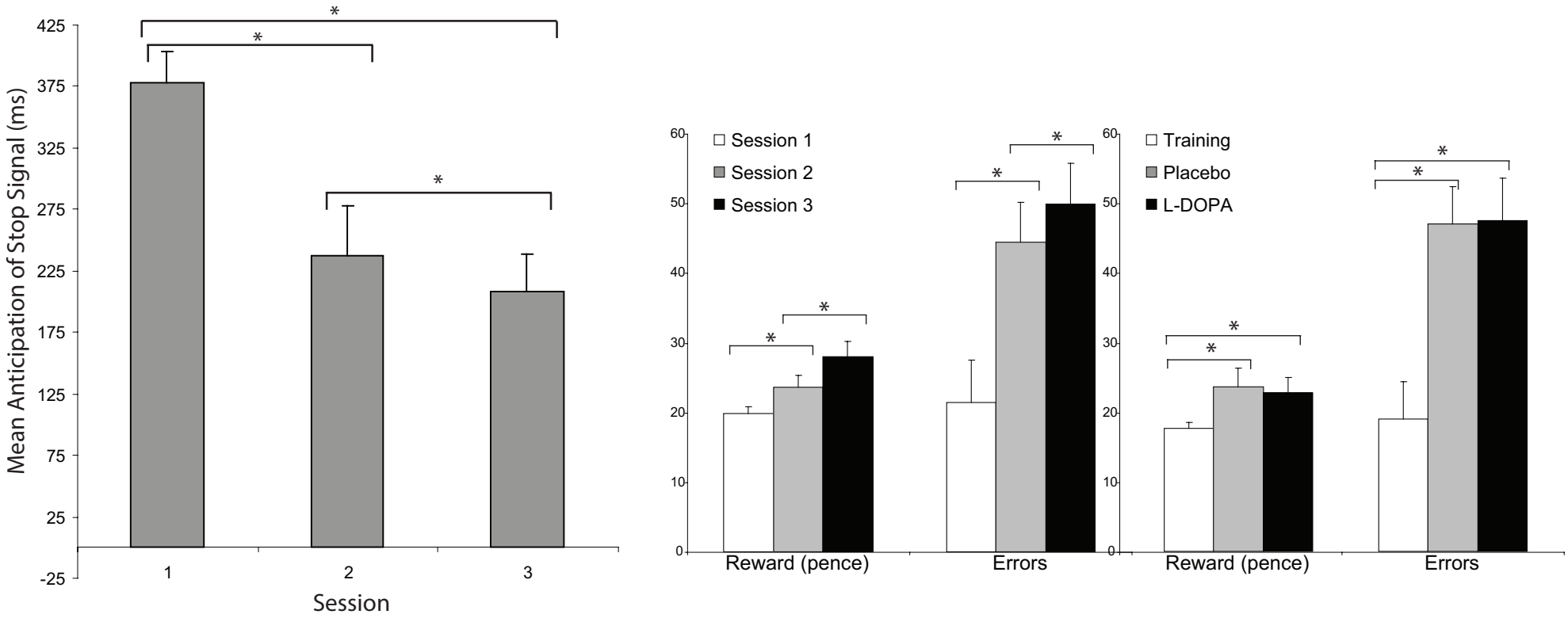



**Figure 5.10 Reverse Traffic Light Mean STOP anticipation**

**Left:** Across the sessions, subjects took greater risk by increasing the time they were prepared to wait before making their response (thus *reducing* the STOP anticipation interval).

**Right:** This led to increased errors but also increased reward overall. There is a statistically significant improvement in reward and associated increase in errors (indicating a rightward shift of the response distribution) across each session.

**Statistically Significant Difference*

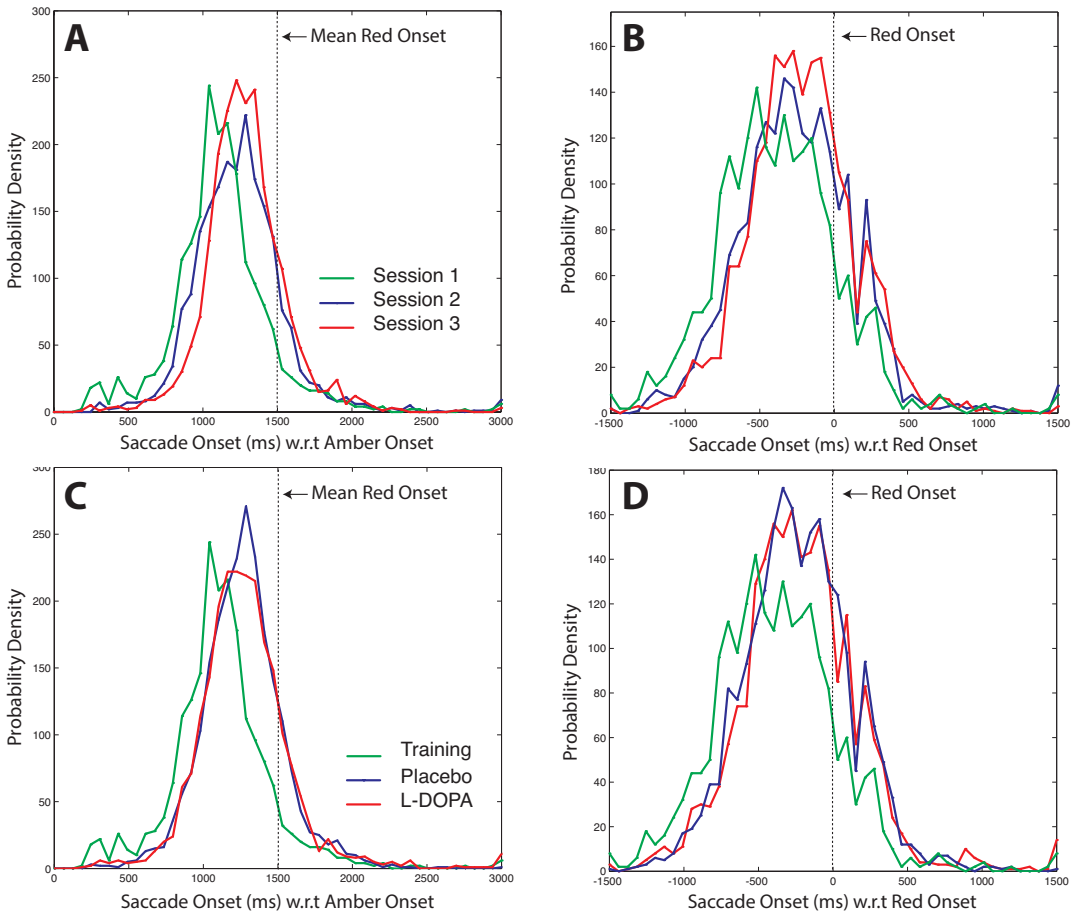



**Figure 5.11 Reverse traffic Light Saccade distributions**

There is a rightward shift of the saccade distributions between training and drug/placebo sessions. There is no main effect of drug versus placebo.

**A** Comparison of saccade distributions across sessions with respect to amber onset;

**B** The same data plotted with respect to Red onset (Stop!);

**C** Comparison of saccade distributions in training versus drug and placebo conditions with respect to amber onset;

**D** The same data plotted with respect to Red onset (Stop!)

### 5.3.5 The Lateral Reward Task

The lateral reward task was not administered in the training session, as it had not yet been developed. Furthermore, only 8 subjects performed the task, as it was introduced part way through the study. There are three variables to consider when interpreting saccadic latencies in this task: the session (2 or 3), the drug/placebo condition (D or P) and whether the saccades were rewarded or not (R or U).

We performed an analysis of variance (ANOVA) to better understand the contribution of L-dopa to reward sensitivity (Fig 5.12): A two factor ANOVA (with replication) of the latencies to rewarded targets demonstrates a significant interaction between drug /placebo condition and session ($F(1,15)$, $p=0.03$).

#### 5.3.5.1 Lateral Reward Task Session Effects

In session 2, there were faster saccades to rewarded targets, as expected (Figure 5.12), however this difference did not reach statistical significance (Unrewarded saccade mean latency, U1 = 222ms; Rewarded saccade mean latency, R1 = 218ms; paired, 1-tailed Student T-test, $t(7)=0.86$, $p=0.21$). In session 3, there were significant differences between saccadic latencies to unrewarded (mean 217ms) and rewarded (mean 205ms) targets (paired, 1-tailed Student T-test, $t(7)=2.29$, $p=0.03$). The magnitude of reward sensitivity/preference therefore increased with learning the task. This learning effect may be more pronounced as a result of the lack of a training session for this task. Comparing unrewarded saccades *between* sessions (U1 mean = 222ms, U2 mean =217ms, paired, 1-tailed Student T-test, $t(7)=1.46$, $p=0.09$) separately from rewarded saccades (R1 mean = 218ms, R2 mean =205ms, paired, 1-tailed Student T-test, $t(7)=3.27$, $p<0.01$), it is clear that although both latencies were reduced in Session 3, the change was greater and statistically significant only for *rewarded* saccades.

#### 5.3.5.2 Lateral Reward Task Drug Effects

In the L-dopa condition, differences between unrewarded (UD, mean=220ms) and rewarded (RD, mean=214ms) saccades were not significant (paired, 1-tailed Student T-test, $t(7)=1.22$, $p=0.13$). However, in the placebo condition, they were (UP = 219ms, RP = 210ms, paired, 1-tailed Student T-test, $t(7)=1.92$, $p<0.05$). This suggests that L-dopa blunts reward sensitivity, rather than heightening it.

Previous studies (Hood et al., 2007; Michell et al., 2006) and our SRT Task results suggest that L-dopa increases saccadic latencies. However, comparing both unrewarded saccades (UP = 219ms, UD = 220ms, paired, 1-tailed Student T-test, $t(7)=0.09$, $p=0.46$) and rewarded saccades (UP = 210ms, UD = 214ms, paired, 1-tailed Student T-test, $t(7)=0.61$, $p=0.29$), there were no significant differences found between the drug and placebo conditions. Saccadic latencies toward *unrewarded* targets are very similar in each condition. However, the latencies are non-significantly *shorter* toward rewarded targets in the placebo condition. This suggests that L-dopa is actually *reducing* reward sensitivity. However, it may be that, rather than a generalised slowing (which would cause increased latencies to both unrewarded and rewarded saccades), we are observing an increase in the *minimum* saccadic latency due to L-dopa. In other words L-

dopa, rather than effecting a simple 'sedative' slowing of reaction times, may set a higher threshold for saccade initiation.

In a comparison of *rewarded* saccades in the 'drug first' and 'placebo first' groups, there were significant differences: In session 1, those who took L-dopa were significantly *slower* toward rewarded targets than those who took placebo (RD1=227ms, RP1 = 209ms, 2-tailed Student t-test, $t(6)=2.70$, $p<0.05$). By contrast, in session 2, those who took L-dopa were non-significantly *faster* than those who took placebo (RD2=200ms, RP2 = 210ms, 2-tailed Student t-test, $t(6)=-1.04$, $p=0.33$). These samples are small (n=4 in each condition), however, the directional difference of the effect suggests that larger samples may reveal an effect of L-dopa upon reward sensitivity in this task and explain the interaction demonstrated by the ANOVA (Figure 5.12A).

### 5.3.4 Correlations with Questionnaire findings

Spearman's rank correlation coefficient was calculated for BIS-11 and TPQ scores with the same performance indicators reported in Chapter 3. Self report measures were not significantly correlated with performance indicators or of drug/placebo responses in the oculomotor tasks.

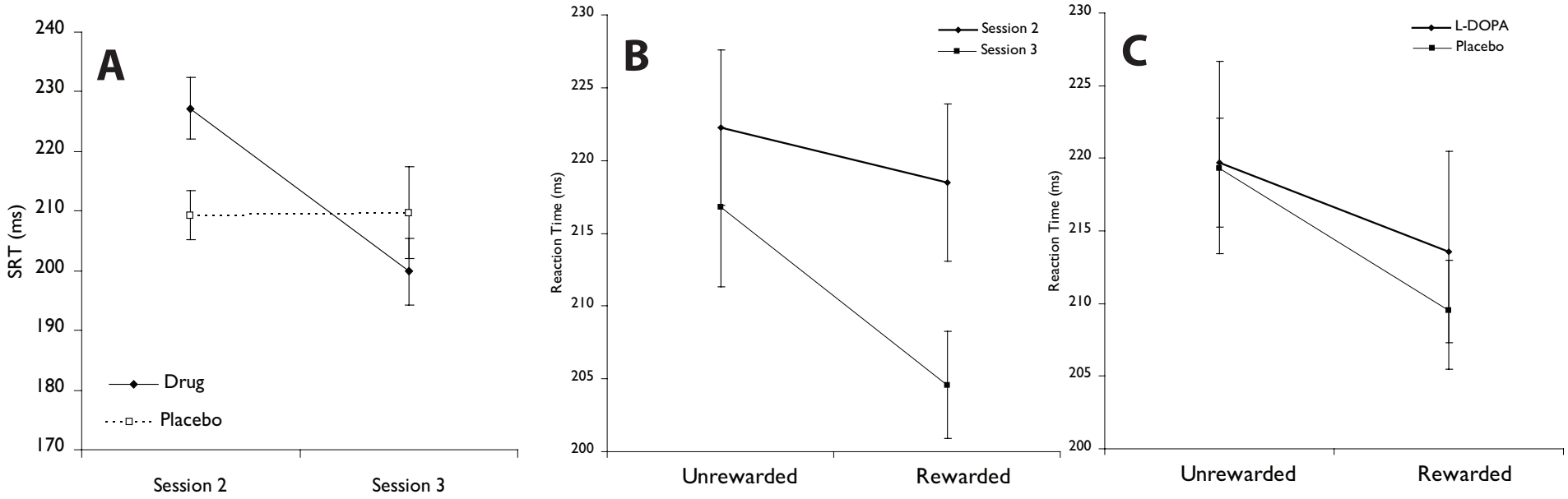



**Figure 5.12 Interaction of drug and session effects upon rewarded saccades**

**A** Those subjects who received L-dopa in the earlier session were slower in responding to rewarded saccade targets than those who received placebo. In the second session, those receiving L-dopa were faster.

**B** In both sessions, there was speeding toward rewarded targets; this was significant in session 3. The magnitude of this difference as well as the overall speed increased from session 2 to session 3.

**C** There was speeding to rewarded targets in both drug and placebo conditions. The magnitude of the difference was non-significantly greater for placebo.

## 5.4 Discussion

This study examined the effects of L-dopa upon eye movement tasks. There were no reported side effects and all enrolled subjects completed the study.

### 5.4.1 Experimental Results

As hypothesised, the effects of training across sessions were prominent, a factor often ignored in drug/placebo experiments. There were improvements in all tasks across sessions. Analysis of variance demonstrated a non-significant interaction between the drug/placebo condition and the session in the SRT task (Figure 5.2), suggesting that the order of drug/placebo administration is important. The drug effect was of slowed responses compared to placebo in the second session, whereas it had no significant effect in the third session. This difference may be due to dopaminergic modulation having specific effects on novel tasks but not previously trained ones. Dopaminergic effects of task novelty on learned responses have been demonstrated by direct physiological recordings from dopaminergic neurons (Schultz et al., 1993).

Analysis of variance in the Traffic Light Task demonstrated a non-significant interaction between drug/placebo condition and session with respect to error rates (Figure 5.7). In the second session, L-dopa appeared to reduce error rates compared to placebo, in the 'drug first group'. Conversely, in the third session, when the 'placebo first' group were given L-dopa, more errors were made than by the placebo group. Training effects upon saccade distributions appeared to plateau after the first session. The effect of training was an increase in anticipatory responding and errors. This was accompanied by a significant increase in reward. Once established (through training), this increased anticipatory response distribution was unaffected by drug (or placebo) administration.

In the reverse traffic light task, designed to assess risk seeking and relatively independent from reaction time, the main effect was, again, of training, with subjects increasingly willing to risk errors in order to reap greater rewards on successful trials. With each session, the distribution of saccades shifted rightward. There was a significant reduction in the mean STOP anticipation (SAI, the degree to which subjects accurately anticipated the red light) between sessions 1&2 and a further significant reduction in Session 3. The task is designed to measure willingness to take risk, as it requires responses to be made *as late as possible* in order to accrue the greatest reward. There was no evidence of a change in risk seeking/avoidance resultant from the drug versus placebo conditions.

In the lateral reward task, there was a significant interaction for latencies to rewarded targets between drug/placebo condition and session (Figure 5.12). It would appear from these results that receiving L-dopa in the first session, enhanced the learning effect, leading to *even faster* responses to rewarded targets in the second session. This is apparent from the mean latencies – the four subjects who received L-dopa first improved from a mean of 227ms to 210ms, whereas those who received placebo first made a smaller improvement from 210ms to 200ms. One might otherwise infer that the 'drug first' group were slowed by L-dopa in the first session but

were able to exploit enhanced learning in the second session, when they were faster and drug free. The 'placebo first' group, by contrast, had no enhanced learning and were slowed down by L-dopa in the second session, leading to an apparent diminished learning effect. Alternatively these findings might represent a "ceiling effect" due to the 'placebo first' group being faster overall by chance. This also raises the possibility of a speed/accuracy trade-off when subjects are administered L-dopa – the first group favouring slower more accurate responses while the second group opted for a faster but more error-prone performance.

### 5.4.2 General Discussion

There are several reasons that might explain the small differences found when comparing L-dopa and placebo- modulated performance on our tasks. The simplest explanation is that saccadic decisions are unaffected by L-dopa at this dose. Otherwise, effects may have been lost due to individual variability in both the direction and the extent of performance difference due to the drug.

#### 5.4.2.1 L-dopa has variable reaction time and dosage effects

The alteration in synaptic dopamine levels due to 100mg of levodopa may be insufficient to instigate changes in reward sensitivity, risk seeking, reaction time necessary to influence oculomotor task performance on our tasks. With larger doses, more marked effects may have seen. However, 100mg L-dopa was found to have the greatest effect (compared to either 25mg or 200mg) on paired associative stimulation induced plasticity, thought to reflect learning related processes (Thirugnanasambandam et al., 2011).

The lack of significant effects on saccadic reaction times in either the SRT task or the Lateral reward task may be due to the dose used (100mg). Previous studies demonstrating manual reaction time effects have used higher doses of L-dopa – e.g. 200mg (Rihet et al., 2002). There is also evidence that repeated doses in drug studies on healthy volunteers are more effective (Knecht et al., 2004). However, consistent with our findings, a previous study using 100mg found no effect upon 'reflexive' saccadic latencies (Duka and Lupp, 1997).

#### 5.4.2.2 Patient and volunteer responses to L-dopa may differ

Extrapolation from patient studies is difficult. It is likely that the long term (tonic) drug effects reported (Cools et al., 2003, 2010) differ from the acute changes seen following administration of a single dose to a drug naive subject. There is evidence that suggests drug naïve PD patients are more susceptible to the cognitive effects of L-dopa than those with a stable response to L-dopa (Kulisevsky et al., 1998). There are possible differences in patients' endogenous dopamine levels and dopamine receptor numbers/activity as a result of chronic drug administration. Previously reported effects of an L-dopa induced increase in saccadic latency (using the patients' usual doses) in PD patients (Hood et al., 2007; Michell et al., 2006) may be due to these differences, or dose effects. Furthermore, in antisaccade tasks, L-dopa has been found to cause opposing effects in PD patients, who made fewer errors (Hood et al., 2007), and healthy volunteers, who made more errors (Duka and Lupp, 1997). Nevertheless, the trend in our results was for faster responses in the placebo rather than the L-dopa condition consistent with the patient studies,

and it is possible that with larger subject numbers, higher, or repeated dosing we might have replicated those findings.

#### 5.4.2.3 There may be independent optimal levels of dopamine for both individuals and tasks

Animal experiments have demonstrated large individual variation in both the direction and extent of drug effects. Experiments demonstrate the "law of initial value" wherein pharmacological manipulation of blood pressure and heart rate depended upon the baseline of the tested variable (Wilder, 1962). Similarly, the effects of dopaminergic drugs on cognition depend upon baseline levels of performance (Robbins and Sahakian, 1979; Kimberg et al., 1997; Mehta et al., 2000; Granon et al., 2000; Mehta et al., 2004). In other words, a dopaminergic drug may improve poor baseline performance in a given task, whereas good performance may be impaired. If this were the case in our study, we might expect analysis of poor performers in the training session to reveal different outcomes from those who performed better at baseline. A larger study would be required to demonstrate such differences. However, other animal and human experiments also demonstrate that simplistic 'inverted-U-shape' relationships between DA levels and performance are insufficient to explain or predict performance on cognitive tasks (Cools, 2006). Within a single subject, some functions will be enhanced and others impaired by the same drug dose. There is therefore task as well as an individual variation in the response to these drugs.

Recent research has shown that risk taking is associated with DAT1 polymorphisms when subjects perform the Balloon Analogue Risk Task (BART, see Chapter 3 (Mata et al., 2012)). It is also known that genetic variability can affect the response to L-dopa (Eisenegger et al., 2010): A high dose (300mg) of L-dopa was administered to a very large group (n=200) of healthy volunteers who had been genotyped for DRD4 polymorphism. Without considering D4 subtypes, L-dopa had no effect upon gambling propensity. However, division by genotype found increased gambling tendency in those carrying at least one copy of the 7-repeat allele. It is therefore possible that a genetically heterogeneous group might demonstrate opposing effects of the drug. There may also be underlying dopaminergically derived individual differences in the amount of effort people are willing to expend for rewards (Treadway et al., 2012). These effects might, when superimposed, cause regression to the mean.

#### 5.4.2.4 Differential learning effects due to the order of drug/placebo presentation

Analysis of variance demonstrated similar interactions of drug/placebo condition and session in SRT (interaction not significant) and Lateral Reward (interaction significant) tasks. There was also a non-significant interaction with regard to the number of errors in the Traffic Light task. Such interactions may indicate an enhanced training effect due to dopamine in the earlier session, or a chance ceiling effect due to the 'placebo first' group being faster to start with. A study using methylphenidate found that the drug *enhanced* performance on spatial tasks from the CANTAB battery (Robbins et al., 1994b) when taken in the first session but *impaired* performance and reduced response latency if taken in the second session (Elliott et al., 1997).

#### 5.4.2.5 L-dopa modulates reward sensitivity

The lateral reward task is a measure of reward sensitivity. L-dopa administration non-significantly attenuated reward sensitivity. It is possible that this apparent difference is due to reaction time effects, in that L-dopa could be creating a 'cap' on the maximum saccade speed. Alternatively, excessive dopamine may impair an already optimal dopaminergic state, thereby reducing reward responsiveness. This may contrast with PD patients, in whom reward sensitivity might be optimised by exogenous dopamine administration. L-dopa withdrawal studies have demonstrated that the drug improves cognition in some patients, but causes deterioration in others (Gotham et al., 1988). Consistent with the inverted U-shape hypothesis, patients who were performing particularly poorly off the drug gained the most benefit from L-dopa, whereas those who performed well off drug were impaired by its administration. This finding has lead to the so-called "Dopamine overdose" hypothesis (Vaillancourt et al., 2013) . This suggests that the doses of L-dopa required to replace endogenous neurotransmitter in damaged brain areas lead to an *overdose* of other (intact) brain areas.

#### 5.4.2.6 More potent dopaminergic modulation or alternate agents may have greater impact upon oculomotor decisions.

It is possible that drugs with greater DA receptor subtype specificity might prove more effective in modulating response to our tasks. Many of the reported examples of drug effects on decision making in both healthy volunteers and PD patients have used DA agonists, D2 agonists in particular (Frank et al., 2004; Cools et al., 2007, 2009). This is consistent with the finding of a greater incidence of impulse control disorder in PD patients treated with DA agonists than those treated with L-dopa alone (Grosset et al., 2011). The relationship between specific pharmacological agents and task effects is complex; agents within the same class have been shown to have opposing effects. For example, bromocriptine has been shown to affect cognitive flexibility (in dual-tasking and Wisconsin card Sorting Task) but not simple delayed-response task (Kimberg et al., 1997; McDowell et al., 1998). Pergolide, on the other hand, modulated delayed-response tasks but did not affect set-shifting (Kimberg and D'Esposito, 2003).

Further experiments might consider the use of dopamine agonists, with greater DA receptor specificity and/or stimulant drugs that are more potent in acutely altering synaptic DA levels. The next chapter will discuss oculomotor experiments using a potent DA reuptake inhibitor, methylphenidate.

# 6. The effects of methylphenidate on oculomotor decisions

## 6.1 Introduction

In attempt to provoke a greater dopaminergic response in our healthy volunteer experimental subjects, we used an alternative compound to L-dopa; methylphenidate.

### 6.1.1 Methylphenidate: Pharmacology

MPH belongs to the piperidine class of compounds and increases the levels of dopamine (DA) and norepinephrine (NA) in the brain through reuptake inhibition of the monoamine transporters (Booij et al., 1997; Volkow et al., 1998, 2004). MPH also increases the *release* of DA and NA. Both of these mechanisms cause an increase in extra-striatal dopamine concentrations (de Haes et al., 2007; Montgomery et al., 2006). Imaging studies have demonstrated that this is associated with reduced prefrontal cortex activation (Mehta et al., 2000; Schweitzer et al., 2004). Furthermore, PET imaging has demonstrated that therapeutic doses of MPH significantly increase extracellular DA in the basal ganglia (Volkow et al., 2002).

### 6.1.2 Methylphenidate: Clinical and Experimental Effects

Methylphenidate (MPH) is a psychostimulant drug approved for treatment of attention-deficit hyperactivity disorder, postural orthostatic tachycardia syndrome (Kanjwal et al., 2010), and narcolepsy (Mitler, 1994). It has also been used to treat apathy (Marin et al., 1995; Galynker et al., 1997; Jansen et al., 2001; Hardy, 2009). Clinical research has demonstrated that MPH can *reduce* abnormal risk taking behaviour in patients with frontotemporal dementia (Rahman et al., 2006). More recently, it has become one of the handful of drugs taken, often without prescription, as 'cognitive enhancers' by whose who are medically well, in the hope of improved academic or work performance - or simply to remain awake (Maher, 2008; Swanson and Volkow, 2008; Repantis et al., 2010; Husain and Mehta, 2011; Smith and Farah, 2011; Linssen et al., 2014a).

### 6.1.3 Stimulant behavioural effects are variable and task dependent

We might infer some hypotheses of MPH behavioural effects from animal studies. However, these show variable effects: A comparison of atomoxetine and methylphenidate in rats performing a 5 choice serial reaction time task (5-CSRTT) found that methylphenidate improved overall attention but that the highest dose also significantly *increased* impulsivity (Navarra et al., 2008). By contrast, rats also demonstrated *reduced* impulsivity following MPH administration in a delayed reward task (Vangaalen et al., 2006). There is also evidence of contextual effects: Amphetamine (a stimulant with similar effects to MPH), increased preference for the large/risky option when probabilities *decreased* over a session, but had the opposite effect if probabilities *increased* (St Onge et al., 2010). This demonstrates a task-dependent effect of stimulants upon decision-making under risk.

### 6.1.4 MPH effects on tasks of response inhibition

In humans, MPH has been found to cause "low level" effects such as the speeding of simple reaction times – particularly for more complex responses - and reductions in errors (Hermens et al., 2007; Naylor et al., 1985). MPH also reduced go-trial reaction time in a stop-signal reaction time (SSRT) task (Eagle et al., 2007). Similarly, MPH led to shortened reaction times in a

memory-scanning task, (Fitzpatrick et al., 1988). In a spatial Go/Nogo task under MPH ) faster reaction times and a trend towards less impulsivity errors under MPH vs. placebo were observed (Kratz et al., 2009). There is further evidence to support "higher level" cognitive effects too – in addition to faster processing: An fMRI study using two versions of the stop-signal task to assess the effects of a 40mg dose of MPH (Pauls et al., 2012) found that MPH improved inhibitory performance in association with significantly reduced activation of regions within the right inferior frontal gyrus/insula to infrequent stimuli associated with successful inhibition, failed inhibition, and attentional capture – implying improved concentration /reduced distractibility.

### 6.1.5 MPH may have effects on other higher processes

Evidence of *subject-independent* effects of MPH are reported in a study of cognitive ability and decision-making: This study compared the response of ADHD diagnosed adults and healthy controls: In *both* groups MPH (15mg, adjusted for body mass extremes) was associated with an increase in digit span compared to placebo. However, there was no effect upon decision-making in either group (Agay et al., 2010).

There is some evidence of MPH induced improvement in "performance monitoring" (Hester et al., 2012): A single dose of methylphenidate (30mg) significantly improved the ability of healthy volunteers to consciously detect performance errors. This behavioural effect was associated with a strengthening of activation differences in the dorsal anterior cingulate cortex and inferior parietal lobe during the methylphenidate condition for errors made *with* versus *without* awareness.

MPH higher-level effects may be context and/or task dependent: In a study wherein subjects underwent fMRI during a Go/Nogo task and a tracking stop-signal task after administration of 40mg MPH or placebo (Costa et al., 2013), results revealed both task and condition-specific effects of MPH: There was increased activation in the putamen only during inhibition *errors* but not during successful inhibition and only in the Go/Nogo task. It is possible that task specificity of the effect might be due to differences in the degree of error *saliency* in the task designs. Errors were few in the Go/Nogo task and thus had high saliency and the stop-signal task was designed to elicit 50% of errors in all subjects, diminishing the error saliency effect. The findings suggest that neural MPH effects interact with the saliency of the behaviour under investigation.

Beneficial effects of MPH (20 and 40mg) have been demonstrated in healthy volunteers using tasks sensitive to frontal lobe damage (Elliott et al., 1997). Methylphenidate had significant effects on performance of the tests of spatial working memory and planning. However, there was an interaction between the drug/placebo state and the session order: When the drug was taken on the first test session, performance on the spatial tests was enhanced. When the drug was taken second, performance accuracy was impaired whereas response latencies were decreased. These results are consistent with a hypothesis that methylphenidate influences performance in two conflicting ways; enhancing executive aspects of spatial function on novel tasks but impairing previously established performance.

A review and meta-analysis of 46 studies of MPH looked for effects upon motivation, wakefulness, attention and vigilance (Repantis et al., 2010). The authors also found that no consistent evidence was available for any "neuroenhancing" effect of MPH: For single dose administration, the main discernable effect was on memory – with a significant improvement found. No main effects upon attention, mood or executive function were found in the meta-analysis. Imaging studies suggest an important role for dopaminergic effects of MPH (40mg) in increasing the speed of processing of uncertainty (but not the choice outcome) in decision making tasks (Schlösser et al., 2009). However, given this lack of change in the decision outcome, the behavioural importance of changes in cerebral blood flow remains unclear. More subtle (or complex) cognitive effects may be less amenable to experimental modulation with MPH: No main effects of the drug on a continuous performance task, a short-term memory task or cognitive rating scales were found in 12 healthy adult volunteers given 0.3mg/kg MPH (Aman et al., 1984).

### 6.1.6 Methylphenidate: Eye Movement Effects

The majority of studies of methylphenidate's cognitive effects are reported in patients with ADHD. Given the "paradoxical effect" of stimulant medication in this condition (Robbins and Sahakian, 1979), results must be interpreted with caution. ADHD without medications causes abnormalities in various saccadic tasks (Mostofsky et al., 2001) including decreased SRT for pro-saccades, delayed voluntary anti-saccades, increased intra-subject variance (Munoz et al., 2003) and impaired response inhibition in a memory guided saccade 'oculomotor delayed response' task (Ross et al., 1994). No saccadic or other eye movement effects upon healthy volunteers are reported to date. Specific investigation of drug-related oculomotor effects in ADHD is also limited. Methylphenidate (10mg) was found to reduce both pro- and anti-saccadic reaction times, error correction times and the proportion of direction errors in an anti-saccade task when given to 27 boys with ADHD (Klein et al., 2002). Another study using oculomotor tasks in ADHD found that MPH improved performance in both motor planning and response inhibition (O'Driscoll et al., 2005).

### 6.1.7 Summary

Methylphenidate may improve simple motor performance by improving attention and reducing reaction times. However, cognitive effects are complex, vary *between* individuals and also *within* individuals according to the task being performed, the degree of novelty, saliency of e.g. errors and the drug dosage received. Few studies have investigated the effects of MPH on healthy volunteers, and none that we know of have looked at MPH on human eye movements. Given the effects on reaction time and inhibition, I hypothesized that MPH might influence performance on oculomotor decision making tasks.

The same crossover design and experimental protocol was used as that described in Chapter 5 on L-dopa. Due to the lack of a main effect of drug in that study, twice as many subjects were tested in order to increase the power of this experiment.

## 6.2 Methods

30 right-handed healthy volunteers were recruited of whom 24 (12 female, mean age 23.1yrs, SD 4.1) went on to complete the study.

Subjects were asked to fast for four hours prior to their testing session to ensure an empty stomach, with the aim of increasing the speed to reach peak plasma MPH concentration (Kimko et al., 1999). Training sessions were conducted at a prearranged time. This time was kept as the start of testing for drug and placebo sessions. These were held at the same times, one and two weeks after training (randomised counterbalancing of the order was planned in advance).

We used the same experimental protocol as for the L-dopa study. Some participants (n=2) participated in both studies. In that case they did not receive a further training session, as they were already familiar with the tasks. The two studies were sufficiently separated in time that any very specific latency related procedural memory was unlikely to have persisted from the prior drug study.

We tested each subject on 3 separate occasions. Many drug/placebo studies fail to account for the effects of training on their measures. We wished to reduce the influence of sessional training effects upon our main interest; the drug versus placebo comparison. To this end, we trained each subject prior to drug and placebo sessions.

Each subject was randomly assigned to receive drug or placebo in the second session and the remaining placebo or drug in the third. Pre-randomisation was achieved by ensuring that a set of drug containers contained an equal number of 'drug-first' and 'placebo-first' options. The experimenter was kept unaware of the order until the study and analysis were complete. Subjects were also blinded, as the drug and placebo preparations were not easily distinguished and had no identifying markings. At the end of the study, there were an equal number in the 'drug-first' and 'placebo-first' groups.

This counter-balanced, crossover design allowed observation of both *training effects* across the 3 sessions and also comparison of the effects of *drug versus placebo*, independent of any training effect. We could also infer effects of drug and/or placebo upon learning.

Subjects were asked to fast for four hours prior to their testing session to ensure an empty stomach, therefore increasing the speed to reach peak plasma MPH concentration. Sessions were conducted at a prearranged time. This time was kept as the start of testing for drug and placebo sessions which were held at one and two weeks after training. At the training session, subjects were asked to choose a letter from the remaining set of envelopes, and this determined the order of the drug and placebo conditions for the remaining 2 sessions.

The onset of CNS effects occurs rapidly (within 60-90 minutes (Volkow et al., 2002)) following ingestion of methylphenidate and persist for about 4 hours (Wolraich and Doffing, 2004). We therefore chose to commence testing an hour after drug ingestion. Testing was complete within

two hours. We opted to use a similar dose to that employed in a prior successful study on young healthy controls: 60mg (Clatworthy et al., 2009).

### 6.2.1 Experimental Design

When subjects arrived for the second session, they were given a drug container that contained either MPH 60mg (as 3 x 20mg tablets) or 3 multivitamin tablets. Neither tablet imparted any distinctive flavour or colour which would have unblinded the participant or experimenter.
The following tests and tasks were administered during the 2-hour period:

#### 6.2.2.1 Questionnaires

During the training session, subjects completed two questionnaires before and/or during breaks between eye movement testing:

3) The Barratt Impulsiveness Scale (BIS-11). This is a measure that has been used in multiple studies of impulsivity in both health and disease (see Chapter 3 for further discussion).
4) The Cloninger Tridimensional Personality Questionnaire (TPQ, (Cloninger, 1987) (Chapter 3). We hypothesised that there might be an inverse correlation between the Novelty-Seeking (NS) dimension and risk avoidance in our tasks, a positive relationship between the Harm Avoidance (HA) dimension and task risk avoidance and a positive correlation between the Reward Dependence (RD) dimension performance on our rewarded tasks.

#### 6.2.2.2 Eye Movement Tasks

Following drug/placebo administration in sessions 2 and 3, subjects were asked to wait in the lab for an hour before testing commenced. This was to ensure that drug plasma levels reached their peak as testing began. Subjects were free to read, work or use the Internet during this period but were continuously monitored for any side effects. They were also asked not to drink any caffeine prior to or during this first hour, but were offered as much fluid as they wished.

*SRT Task* (See Chapter 2)
Though we believe the anticipatory and reactive distributions of the traffic light task to be independent, we felt it would be important to exclude a simple speeding or slowing effect of drug or placebo *in a reward independent task*. We therefore designed a task-relevant saccadic reaction time (SRT) task.

This required subjects to make eye movements *as fast as possible* when a red STOP signal changed to a green GO signal. The delay from red to green on each trial varied randomly between 500 and 1000ms (rectangular distribution). This task was not rewarded. The saccades required alternated between a rightward saccade (odd numbered trials, from -10 to +10 degrees), and a leftward saccade (even numbered trials, +10 to -10 degrees). Confirmation of a completed saccade was acknowledged by an auditory "ping" and by the cruciform target changing from white to red. Erroneous, early saccades caused an aversive "beep" and the trial to repeat.

*Traffic Light Task* (See Chapter 2).

Subjects were asked to make as much money as possible by making saccades *as quickly as possible* in response to a traffic light stimulus. Each trial begins with a red light that, after 1000ms, turns amber. The amber duration varies randomly from trial to trial and is drawn from a normal distribution (mean 750ms, SD 125ms). Following the amber light, a green GO signal appears. Subjects then made a saccade from the stimulus to a cruciform target at 20 degrees retinal eccentricity. Trials alternated between left to right (odd numbered trials) and right to left (even numbered trials). Correct saccades were rewarded with either a "ping" for latencies of >=200ms or a "Kerching" for latencies of <200ms. Reward was displayed at the target location for each trial and a cumulative total was displayed immediately below the target.

The reward ($R$) for a successful saccade was calculated by an exponentially decaying discounting function in the form:

$$R = ae^{-\left(\frac{t-t_0}{k_1}\right)}$$

Where $a$ = 150, $k_1$=100 and $t$ represents the saccade onset time relative to green onset ($t_0$, milliseconds).

Erroneously early saccades, before the GO signal were punished by an aversive "bleep" and a fixed negative reward of -10 pence.

Studies in similarly aged healthy volunteers had already demonstrated that this task elicited a bimodal distribution of saccadic responses (See Chapter 1). We were interested in the effects of MPH upon the distribution of 'reactive' and 'anticipatory' saccades.

*Reverse traffic Light (Go!) Task* (See Chapter 3)

The *forward* traffic light task tests multiple subject variables, including reaction time, reward sensitivity and risk aversion. We therefore sought to introduce other tasks that investigated each of these in turn.

The reverse traffic light, or "Go!, task was developed in order to look at risk avoidance, independent of reaction time. In this task, subjects were asked to accrue as much as reward as possible. To do this, they had to fixate a traffic light stimulus that was green at the start of each trial. After 1000ms it turned amber. The amber duration was randomly chosen on each trial from a normal distribution (mean 1500ms, SD 250ms). [This was deliberately different from the *forward* traffic light task, to avoid learning effects causing an interaction between the two tasks. The task was also presented before and after the forward traffic light task to minimise interaction effects].

After the amber light, a red STOP signal would appear. If subjects made no saccade prior to red onset, they received a fixed -10 pence penalty and heard an aversive "bleep". The aim was to wait *as long as possible*. The later in the amber light subjects made their saccade, the greater the

reward they received. In other words, subjects were trying to anticipate the red light but ensure that they responded before it appeared – similar to "playing chicken".

Successful anticipation of the red light was rewarded in a similar fashion to the forward task except that the reward *increased* exponentially as the red light onset approached. The reward calculation was necessarily slightly more complicated in this task, as the distribution had to be 'fitted' into a variable amber light duration. This ensured that the reward was always a maximum of 150 pence but meant that reward varied both as a function of the anticipatory interval and the length of the amber light on each trial.

$$R = ae^{\left(\frac{t-t_0}{k_1}\right)}$$

$a$ = 150, $k_1$=100 and $t$-$t_0$ represents the interval time from saccade onset ($t_0$) to the chosen red onset for that trial (t) in milliseconds.

*Lateral Reward Task* (See Chapter 3)
The lateral reward task was adapted from a task designed to look at reward sensitivity in non-human primates (Hong and Hikosaka, 2008). We used our version of this task to investigate effects of MPH versus placebo in affecting reward sensitivity.

In this task, subjects were asked to attend a central white fixation spot. After 1000ms, the fixation disappeared and an identical target appeared at either -10 or +10 degrees retinal eccentricity (this varied randomly from trial to trial, 50% of targets were leftward and 50% were rightward). To begin with, either leftward *or* rightward targets were rewarded according to saccade latency. Reward was presented numerically with a pound coin symbol at the target location and subjects heard an auditory reward similar to that in the traffic light task ("ping" SRT>=200ms, "Kerching!" for SRT<200ms). Saccades to targets on the non-rewarded side were acknowledged with a change in colour of the target (white to red) and a non-rewarding "bleep".

After a jittered number of trials, the rewarded side would switch. On average, 60 leftward trials were presented and 60 rightward. On average, 30 each of these would have been rewarded target locations. The reward side 'switch' occurred approximately every 20 trials (5 switches per 120 trials).

The following experimental protocol was followed*:

| | |
|---|---|
| Time (t) = 0 minutes | |
| | Written consent & Drug (Methylphenidate 3 x 20mg tablets [60mg total]) / Placebo (3 x Multivitamin tablets) Ingestion |
| | Subjects were weighed |
| t = 60 | SRT task (100 trials) |
| | Lateral Reward task(120 trials) |
| | Reverse traffic Light Task (100 trials) |
| | Traffic Light Task (10 blocks x 50 trials) |
| | Lateral Reward task (120 trials) |
| | Reverse traffic Light Task (100 trials) |
| t = 120 | Testing complete, feedback to subjects, debrief and reward payment |

*Except during the training session, when subjects completed the BIS-11 and the TPQ before proceeding immediately with the eye movement tasks.

## 6.3 Results

### 6.3.1 Questionnaires

The mean BIS-11 score for all subjects was 67.1 (SD 9.67) – non-significantly higher than the L-dopa study group (mean 60.2, SD 11.3; Chapter 5), perhaps reflective of the personalities of subjects more likely to volunteer for a trial using a more potent agent. No significant differences were found between BIS-11 scores (or component dimensions of the BIS) when the genders were compared. The mean scores for the three dimensions of the TPQ were: Novelty Seeking 19.3 (SD 4.5), Harm Avoidance 11.7 (SD 3.9) and Reward Dependence 18.6 (SD 1.7). The mean scores in each category were consistent with normal ranges from previous studies e.g. (Otter et al., 1995) and with those found in the experiment described in Chapter 5.

### 6.3.2 SRT Task

A two-way ANOVA (with replication, Figure 6.1) revealed no significant interaction between session and drug condition ($F(1,44)=1.01$, $p=0.32$) for reaction time in the SRT task. There was a non-significant speeding effect of MPH on saccadic latency ($SRT_P$= 300ms, $SRT_D$ = 288ms; paired, two-tailed Student T-test $t(23) =1.05$, $p =0.31$). The main effect, however, was of training. We anticipated this training effect, as it was seen in the experiments described in Chapter 5. Mean SRTs improved from $SRT_1$ = 341ms (SD 72ms) in the training session to $SRT_2$ = 298ms (SD 72ms) in the second session (paired, two-tailed Student T-test $t(23)=2.35$, $p=0.01$). There was a statistically non-significant further improvement in the third session ($SRT_3$= 290ms, SD 66ms; paired, two-tailed Student T-test $t(23)=0.62$, $p=0.27$).

Those who took drug in the second session ($SRT_{D2}$= 301ms) were non-significantly slower than those who took placebo ($SRT_{P2}$= 294ms). Those who took the drug in the third session ($SRT_{D3}$ = 274ms) were faster than those who took placebo ($SRT_{P3}$ =307ms). Neither trend reached statistical significance (this subgroup analysis, n=12, Figure 6.1). Modeling the data using minimum likelihood estimation of parameters ($\mu$, $\sigma$) for a single LATER unit fitted the data well (Figure 6.2 & Table 6.1).

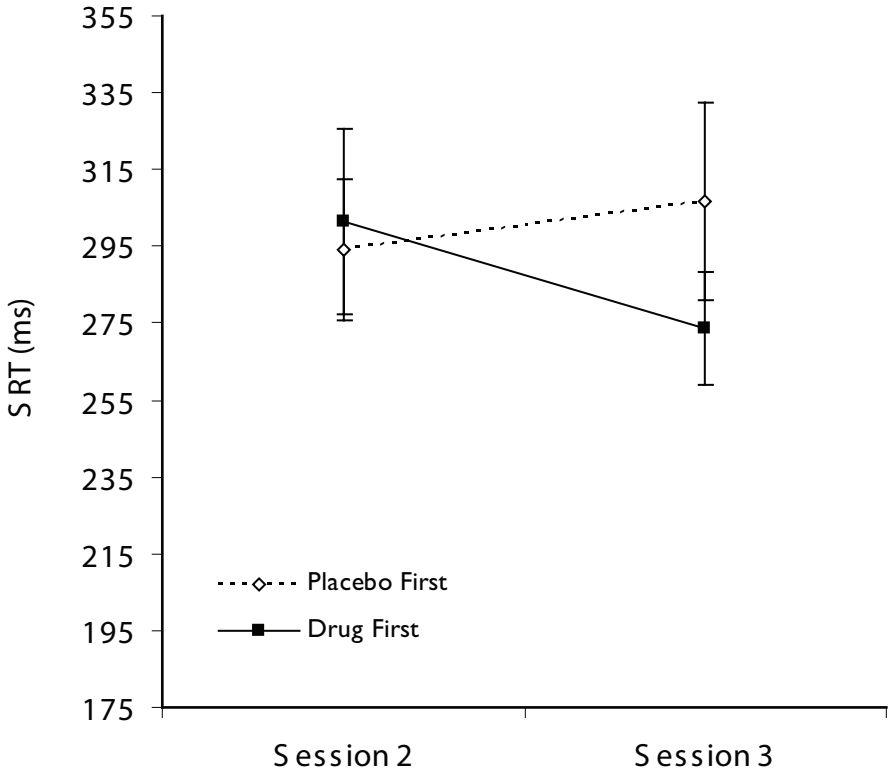



**Figure 6.1 Drug/Placebo & Session order effects on the SRT task**

MPH caused non-significantly shorter latencies overall but the training effect was significant.

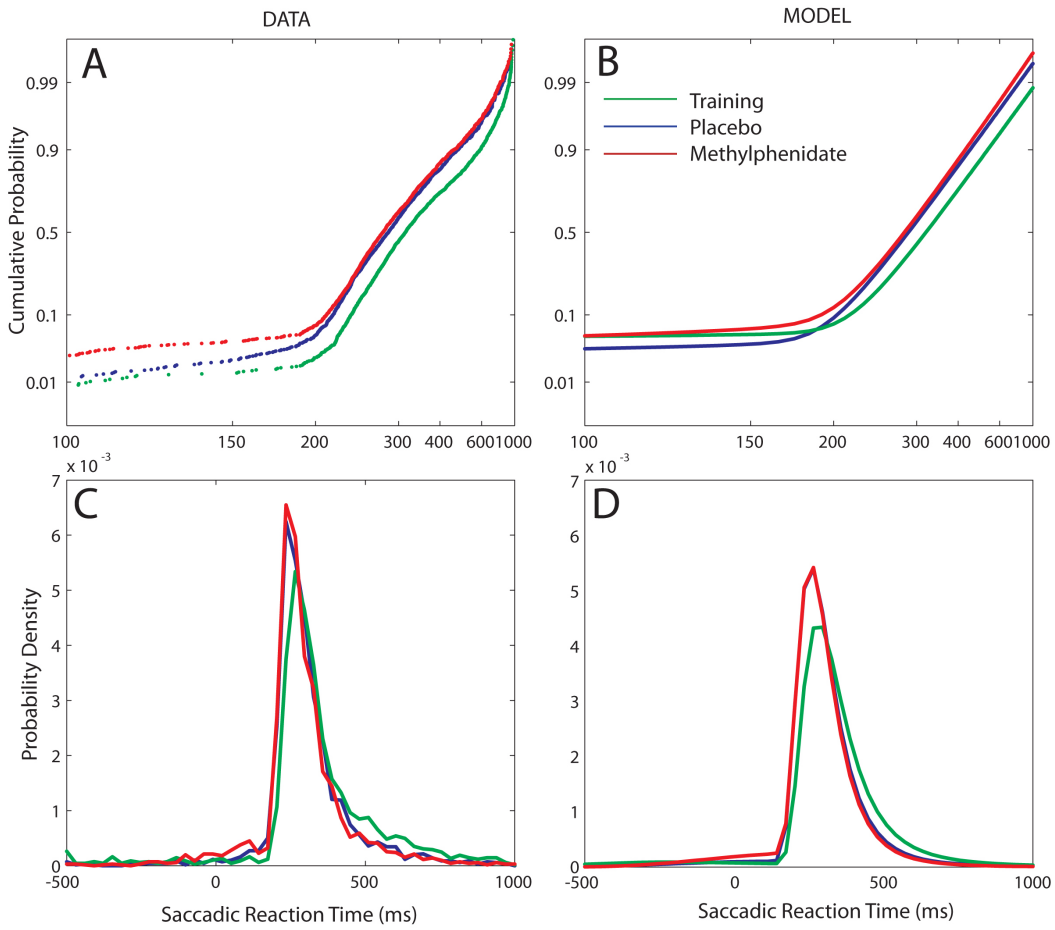



**Figure 6.2 Drug Effects on the SRT task**

SRT response distributions are typically recinormal and differ little from training to drug and placebo sessions. The drug and placebo sessions are, graphically, almost indistinguishable.

A good fit is achieved by minimum likelihood estimation of parameters for a single LATER unit.

**A** Cumulative Saccadic Latency Function (experimental data)

**B** Cumulative Saccadic Latency Function (modelled data)

**C** Probability Density Saccadic Latency Function (experimental data)

**D** Probability Density Saccadic Latency Function (modelled data)

| Session | Mean (median) ms | Modelled Mean |
|---|---|---|
| **1** | 341* (320) | 326* |
| **2** | 298* (289) | 291* |
| **3** | 290 (277) | 291 |
| **State** | **Mean (median) ms** | **Modelled Mean** |
| **Training** | 341 (320) | 326 |
| **Placebo** | 300 (287) | 292 |
| **Drug** | 288 (279) | 290 |

**Table 6.1 SRT Raw Data and modelled distributions**

*There was a statistically significant improvement (reduction in SRT latency) between sessions 1 & 2. However there were no significant differences between other sessions.

### 6.3.3 Traffic Lights

This subject group demonstrated a well-developed anticipatory distribution of saccadic responses to the traffic light task during the training session (Figure 6.3). As a result, the training effect is less marked than in the L-dopa study (Chapter 5). There is no difference between Session 2 & 3 in either raw or modelled saccade distributions. Training effects on Anticipations, Errors and Reward are confined to the sessions 1 and 2 (Figure 6.4). Though effects of drug on these parameters do not reach statistical significance, there is a trend toward *more cautious* behaviour with less anticipation, fewer errors and slightly lower rewards.

Reward significantly increased between sessions 1 and 2 ($R_1$=17.8p, $R_2$=23.9p; paired 1-tailed Student T-test, t(23)=-4.98, p<0.0001) (Figure 6.4). There was a negligible further improvement in session 3 ($R_3$=23.9p; paired 1-tailed Student T-test, t(23)=-0.37, p=0.36). This was due to a significant increase in the mean number of successful anticipatory responses at 0-200ms after green onset ($A_1$=118, $A_2$=157; paired 1-tailed Student T-test, t(23)=-4.02, p<0.001; [$A_3$=157]) and a significant decrease in mean errors ($E_1$=127, $E_2$=109; paired, 1-tailed Student T-test, t(23)=2.04, p=0.03; $E_3$=111).

In order to further investigate possible learning effects of MPH, mean rewards and the corresponding saccadic response latencies were calculated across 5 'epochs' (equivalent to 100 trials, or 2 blocks) (Figure 6.5). In the first session (training), statistically significant improvements in RT and reward occurred between epochs 2 and 3 ($RT_2$ = 209ms, $RT_3$=191ms; 1-tailed, paired Student T-test, t(22)=1.82, p=0.04; $Reward_2$ = 16.0p, $Reward_3$ = 19.4p; 1-tailed, paired Student T-test, t(22)=-2.98, p<0.005). Though improvements occur across all 5 epochs, this is the only one that reaches statistical significance. The epochs in Session 2 are more variable, and although there are statistically significant differences in reward between Epochs 1&2, 2&3 and 3&4, the direction of these differences alternates, suggesting a plateau in the learning and/or the effects of variable attention. In session 3, again there is a significant improvement between epochs 2 & 3, but the general trend is that of a completed learning phase.

Comparing individual reward epochs across sessions, all epochs in Session 1 are significantly less rewarded than they are in either session 2 or 3. There are 2 significant differences when contrasting epochs in sessions 2 and 3: the second and third epochs are both significantly different. Again, the direction (sign) of these differences is different across sessions and the significance is not robust when correcting for multiple (5) comparisons. These results are graphically represented with a table of the relevant data (Figure 6.5 and Table 6.2).

There were no significant differences between any epoch in the drug/placebo condition for either RT or reward (Figure 6.6). There were also no sustained patterns of inter-epoch difference that contribute to any possible change in learning due to either drug or placebo.

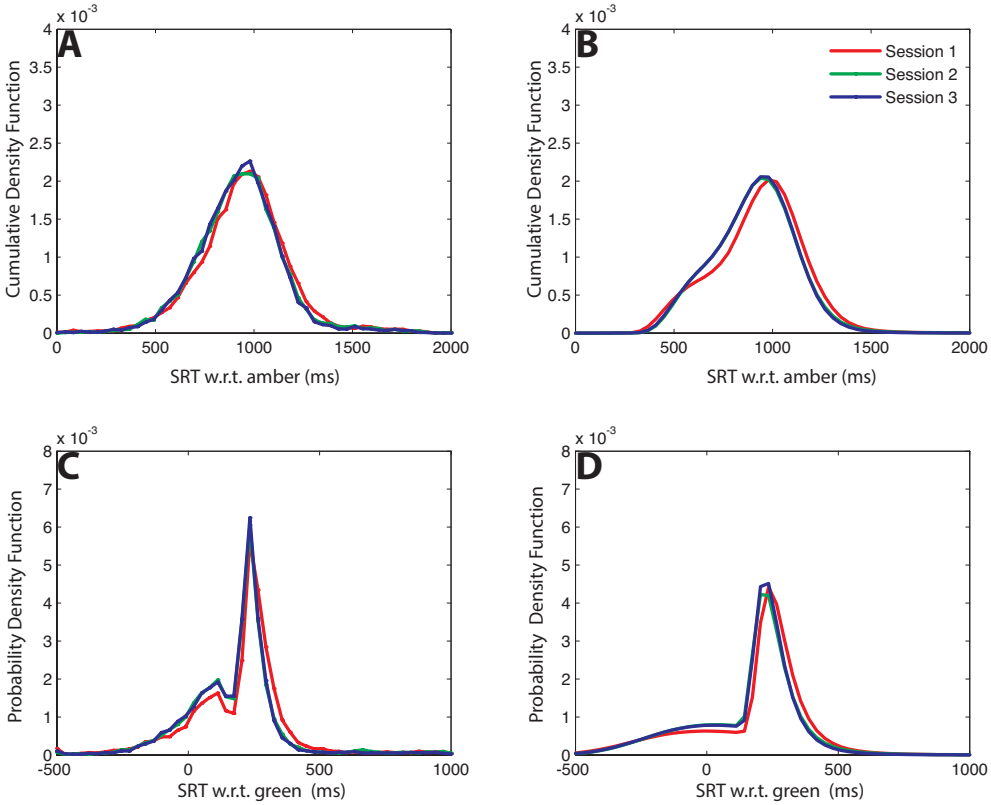



**Figure 6.3 Traffic Light Task Performance: Saccadic Distributions**

Saccade probability density functions plotted against amber (top row) and green (bottom row) light onsets. The raw data is shown on the left, modelled functions on the right. Graphically, there is slightly less anticipation in the first (training) session than in either of the second or third sessions which are almost identical.

**A** Saccade Latency Cumulative Density Function (data)

**B** Saccade Latency Cumulative Density Function (model)

**C** Saccade Latency Probability Density Function (data)

**D** Saccade Latency Probability Density Function (model)

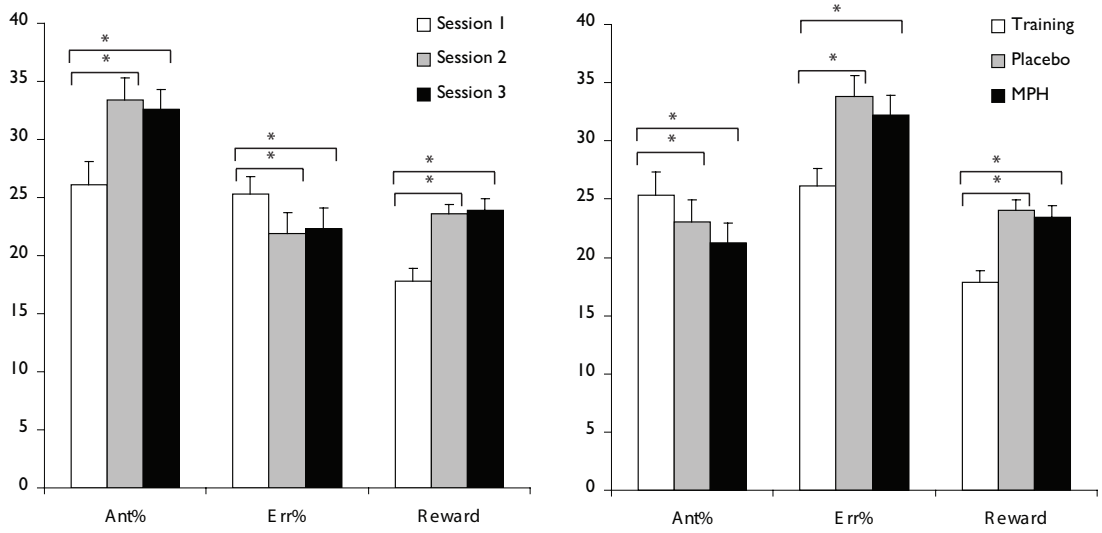



**Figure 6.4 Traffic Light Task Performance: Sessional and conditional effects**

**Left:** On comparing percentage anticipations, percentage errors and reward, there are significant differences between session 1 and session 2 or session 1 and session 3 but not between the latter 2 sessions.

**Right:** Similarly, there are significant differences between the training session and placebo or training session and drug but not between drug and placebo for all 3 variables.

**Statistically Significant Difference*

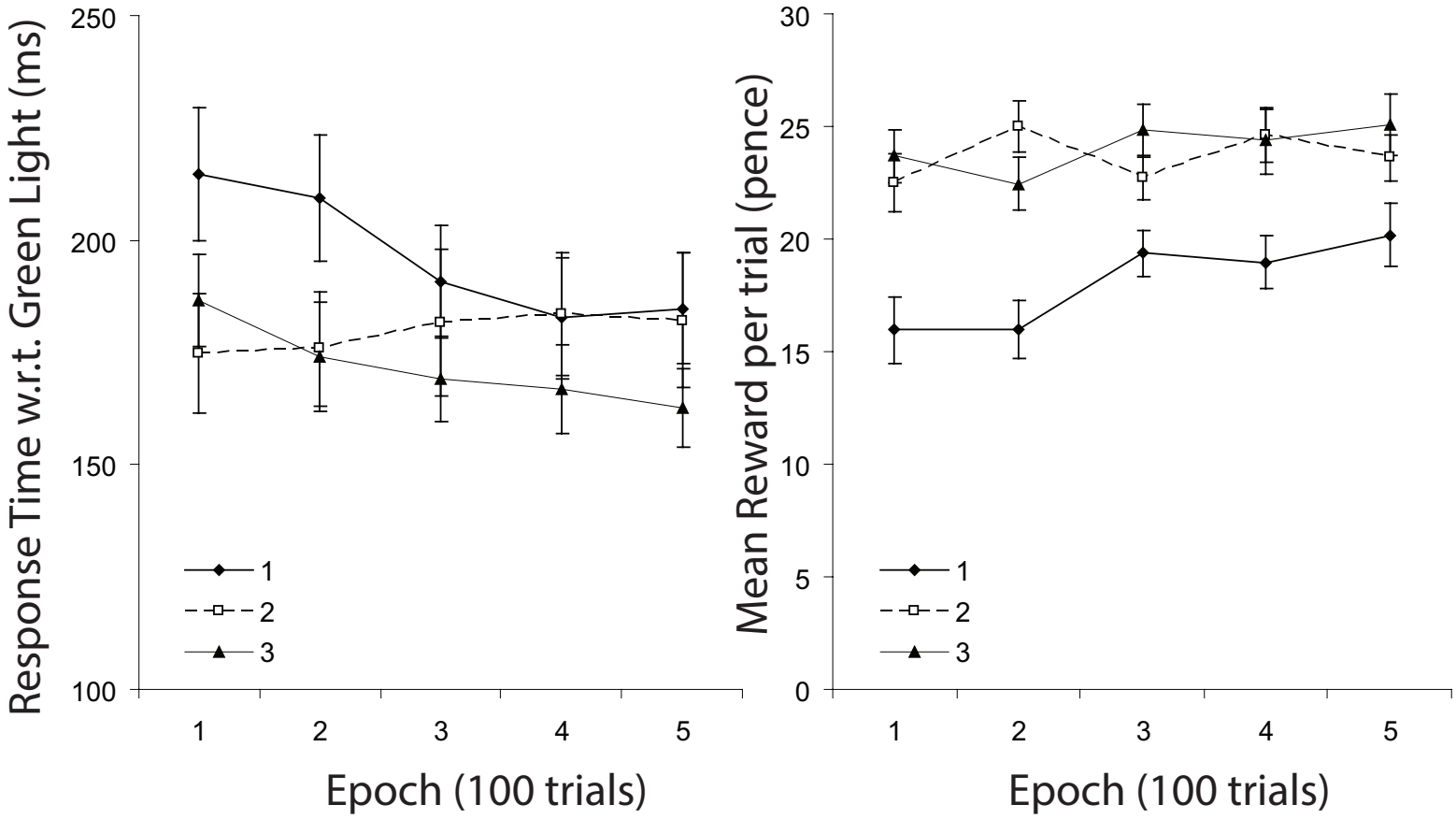



**Figure 6.5** **Traffic Light Task Learning by Session**

In the first session (training), statistically significant improvements in RT and reward occur between epochs 2 and 3. The epochs in Session 2 are more variable, and although there are statistically significant differences in reward between Epochs 1&2, 2&3 and 3&4, the direction of these differences alternates, suggesting a plateau in the learning and/or the effects of sustained attention. In session 3, again there is a significant improvement between epochs 2 & 3, but the overall trend is that of a completed learning phase.

| *Epoch* | *1* | *2* | *3* | *4* | *5* |
|---|---|---|---|---|---|
| **Session 1 RT (ms)** | 215 | 209 | 191* | 183 | 185 |
| **Session 2 RT (ms)** | 175 | 176 | 182 | 184 | 182 |
| **Session 3 RT (ms)** | 187 | 174 | 169 | 167 | 163 |
| **Session 1 Reward (p)** | 16.0 | 16.0 | 19.4* | 19.0 | 20.2 |
| **Session 2 Reward (p)** | 22.5 | 25.0* | 22.7* | 24.6* | 23.6 |
| **Session 3 Reward (p)** | 23.7 | 22.4 | 24.8* | 24.4 | 25.1 |

**Table 6.2 Learning effects within sessions by 100 trial epoch**

*Significant differences from previous epoch (2-tailed T-test, $p<0.05$).

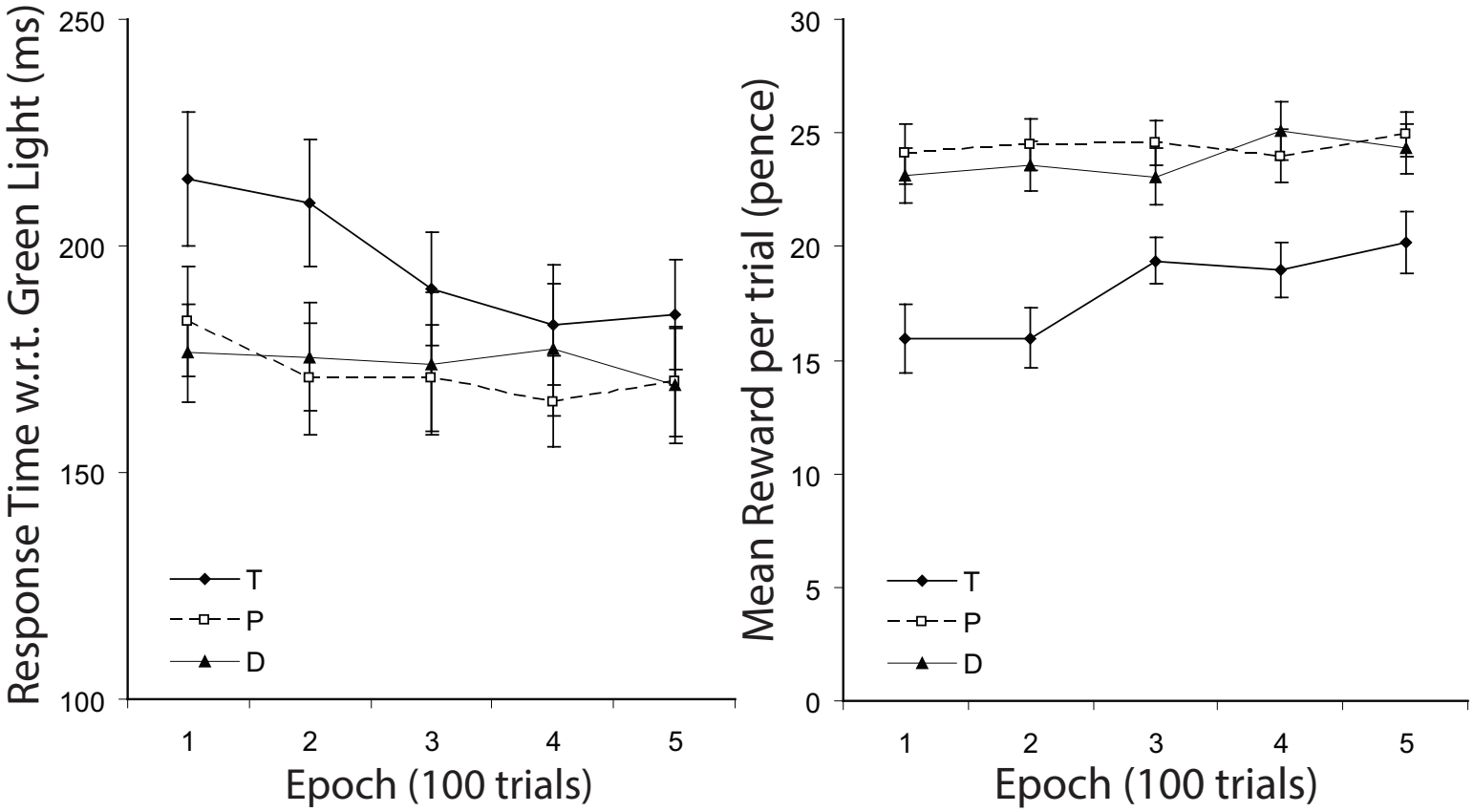



**Figure 6.6 Traffic Light Task Learning by Drug/Placebo condition**

Analysis of the numbers of response times and reward in each epoch by conditions (training/drug/placebo) demonstrated a statistically significant difference between training and subsequent sessions for all epochs but no main effect of drug versus placebo.

*(T=training, P=Placebo, D=Drug (MPH))*

### 6.3.4 Reverse Traffic Light Task

There was a significant improvement in task performance between sessions 1 & 2 (Figure 6.6). The improvement continued but differences were not statistically significant when comparing sessions 2 & 3: The mean stop anticipation interval (SAI, the mean time in advance of the stop signal that a saccade was made) decreased from 370ms (SD 149) in session 1 to 262ms (SD 142ms) in session 2, (paired, 2-Tailed Student T-test $t(23)=3.26$, $p<0.005$). The session 3 SAI was non-significantly lower still at 257ms (SD 130ms) (paired, 2-Tailed Student T-test $t(23)=0.20$, $p=0.84$). This led to significant improvement in reward across the first two sessions: Mean reward session 1 (R1)= 12.90 pence per trial (SD 5.07), R2 = 16.04p (SD 5.25), (paired, 2-Tailed Student T-test $t(23)=-3.11$, $p<0.005$). The mean reward was also non-significantly higher in Session 3 at 18.07p (SD 5.15).

The number of punished trials (errors) also influences reward (Figure 6.6). Errors increased (non-significantly) between sessions 1 (mean 25 errors) & 2 (mean 32 errors), but then decreased again in session 3 (mean 29 errors). This demonstrates that improved accuracy (on correct trials) rather than greater risk taking (which would be evident in a higher error rate) was responsible for task performance improvement.

Though learning effects were evident in comparison of the training session with both drug and placebo conditions (Figure 6.6), there were no significant effects of drug versus placebo state. Therefore, to investigate the interaction between the two, I compared the reward accrued in sessions 2 & 3 between those taking drug first versus those taking placebo first. There was no significant interaction between drug and session effects in a two factor ANOVA with replication.

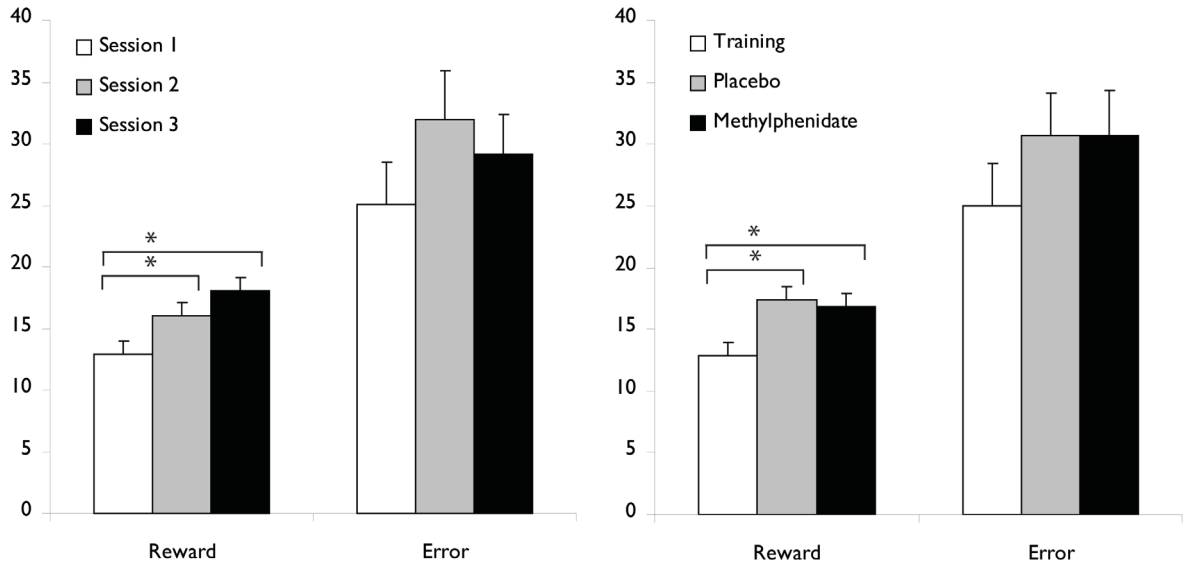



**Figure 6.7 Reward and Error Effects in Reverse Traffic Lights**

There was a significant improvement in task performance between sessions 1 & 2 and between sessions 1 & 3. There was a significant improvement in reward across the first two sessions. The mean reward (non-significantly) higher still in Session 3. Errors increased (non-significantly) between sessions 1 & 2, but decreased again in session 3 (n.s.). This demonstrates that improved accuracy rather than greater risk-taking was responsible for the trend in performance improvement.

*$^{*}p<0.05$*

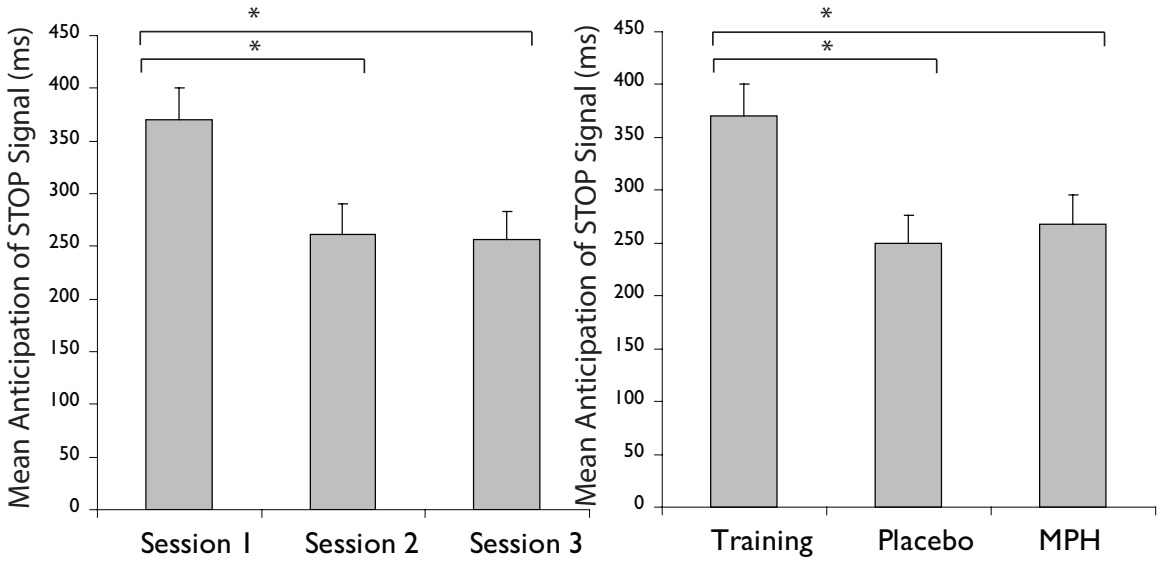



**Figure 6.8 Reverse Traffic Light Task Anticipatory Response Effects**

There was a significant improvement in task performance between sessions 1 & 2 and between sessions 1 & 3. Differences were not statistically significant when comparing sessions 2 & 3: The mean stop anticipation interval (SAI, the mean time in advance of the stop signal that a saccade was made) significantly decreased from 370ms in session 1 to 262ms in session 2. The session 3 SAI was lower still at 257ms. This led to significant improvement in reward across the first two sessions.

*$^{**}p<0.01$*

### 6.3.5 Lateral Reward Task

There were significant differences between rewarded (R) and unrewarded (U) saccade latencies in all sessions, as hypothesised (Figure 6.9 & Table 6.3). (U1=228, R1=221ms, paired, 1-tailed Student T-test, $t(21)=3.94$, $p<0.001$; U2=211ms, R2=202ms, paired, 1-tailed Student T-test, $t(21)=5.01$, $p<0.001$; U3=207ms, R3=194ms, paired, 1-tailed Student T-test, $t(21)=4.59$, $p<0.001$;). There were significant improvements (reductions) in the latency of unrewarded and rewarded saccades in the second session when compared to the first: (U1=228, U2=211ms, 1-tailed Student T-test, $t(41)=2.99$, $p<0.005$; (R1=221ms, R2=200ms, paired, 1-tailed Student T-test, $t(41)=3.46$, $p<0.001$;). There was further, non-significant, improvement in latency between the second and third sessions for both rewarded (R3=191ms) and unrewarded (U3=205ms) saccades, Across the three sessions, the magnitude of the "reward preference" – the difference between mean unrewarded and rewarded saccade latency increased across the sessions (U1-R1=D1=7ms; U2-R2=D2=11ms; U3-R3=D3=13ms). This increase in difference was not statistically significant between consecutive sessions but comparing Sessions 1 and 3 does reach statistical significance (1-tailed Student T-test, $t(42)=-1.87$, $p=0.03$).

There were no main effects of drug (D) versus placebo (P) on the lateral reward task (Figure 6.8 & Table 6.3). There was a significant reduction in latencies to both rewarded (R) and unrewarded (U) targets when compared to the training session (T) (Table 6.3). However, there was no significant difference in saccadic latencies due to the drug or placebo condition (DU = 207ms, PU = 208ms; DR = 196ms, PR = 196ms). There was, however, a persistent significant difference between saccade latencies to rewarded versus unrewarded targets in each condition, as expected from the original experiment (Hong and Hikosaka, 2008). Training (TU =228ms vs TR=221ms), paired, 1-tailed Student T-test, $t(21)=3.94$, $p<0.001$; Placebo (PU =208ms vs PR=197ms), paired, 1-tailed Student T-test, $t(21)=5.46$, $p<0.001$; Drug, (DU =209ms vs DR=197ms), paired, 1-tailed Student T-test, $t(21)=5.01$, $p=0.01$.

### 6.3.6 Correlations

Spearman rank correlation coefficients calculated for BIS-11 and TPQ scores and oculomotor indices demonstrated no relationships with task performance or drug response.

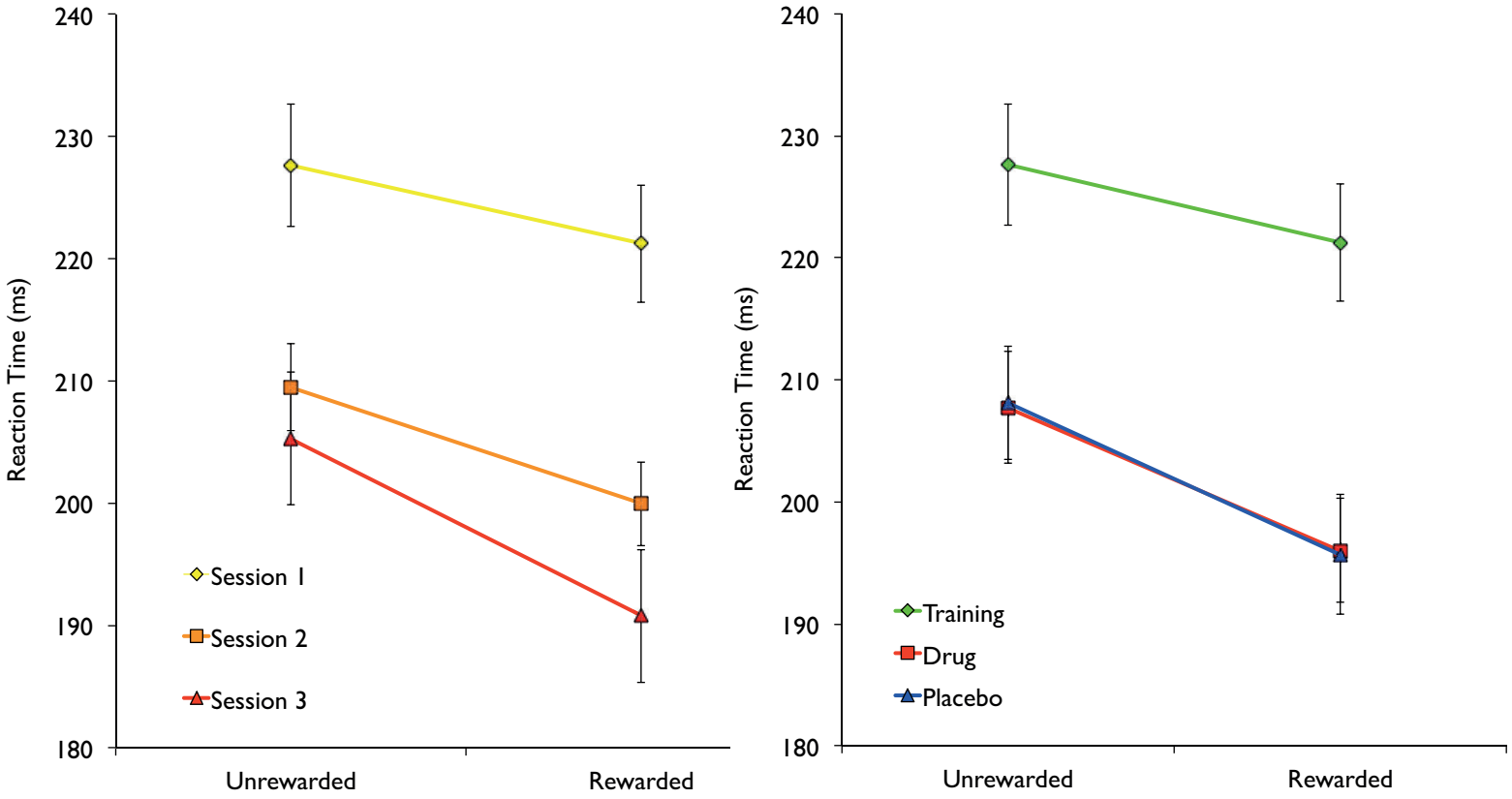



**Figure 6.9 Lateral Reward Task Training and Drug Effects**

There was significant speeding toward rewarded targets in sessions 2 & 3, demonstrating reward preference.

This reward preference increased across the 3 sessions. However, there was no main effect of drug versus placebo.

| *Session* | *1* | | *2* | | *3* | |
|---|---|---|---|---|---|---|
| | **Unrewarded** | **Rewarded** | **Unrewarded** | **Rewarded** | **Unrewarded** | **Rewarded** |
| **Latency (ms)** | 228 | 221 | 211 | 202 | 207 | 194 |
| **Condition** | **Training** | | **MPH** | | **Placebo** | |
| | **Unrewarded** | **Rewarded** | **Unrewarded** | **Rewarded** | **Unrewarded** | **Rewarded** |
| **Latency (ms)** | 228 | 221 | 209 | 197 | 208 | 197 |

**Table 6.3 Lateral Reward Task Response Latencies**

All sessions and conditions demonstrated significant reward sensitivity. There was significant improvement between sessions 1 & 2. Speeding after training to either drug or placebo was significant but there were no significant differences between sessions 2 & 3 or between drug and placebo conditions.

## 6.4 Discussion

This study examined the effects of methylphenidate (MPH) upon eye movement tasks. There were no reported adverse side effects and all enrolled subjects completed the study. Many subjects (20 of 24) reported subjective side effects upon their mood and 3 became somewhat disinhibited during the drug session. These effects diminished within a few hours and were without significant consequence. The analysis was performed while blinded from this information, but both the subject and experimenter may have been inadvertently unblinded by these side effects.

### 6.4.1 Findings

There was a reduction in SRT latency across sessions, as anticipated, with a recinormal distribution, as seen in other simple saccade tasks. Task performance was similar to that seen in healthy volunteers in experiments reported in Chapters 2 and 5. Latencies were non-significantly reduced by MPH compared to placebo, consistent with previous studies which have shown shorter reaction times under the influence of this drug (Klein et al., 2002; Mostofsky et al., 2001). Greater subject numbers might render this a statistically significant effect.

There was a trend toward *fewer* early responses in the Traffic Light Task with methylphenidate (both correct, highly rewarded anticipations and punished errors). This difference did not reach statistical significance. If representative, this trend might reflect a reduction in impulsivity due to methylphenidate (DeVito et al., 2008a) or improvements in timing (Rubia et al., 2009). Learning effects across epochs of 100 trials were similar in the drug/placebo condition, and performance had reached a plateau after the training session. The effects of training were again clearly evident, but there were no main effects of drug/placebo on the stop anticipation or its contingent reward.

There was a consistent finding of reward-sensitive speeding in the lateral reward task. There was significant improvement following training but no difference between unrewarded and rewarded saccade latencies due to methylphenidate.

### 6.4.2 General Discussion

There are a number of possible explanations for the lack of main effect of drug versus placebo in this experiment (other than that the drug simply had no effect on the measures used). An alternative argument might contend that there were effects of different directions on subjects at either extreme of baseline measures. For example, due to a genetic variation in the dopamine transporter gene (DAT1) which may alter the response to stimulant medications (Lott et al., 2004). This could cause regression to the mean in a genetically heterogeneous group. There is also evidence that low doses of MPH may improve function in various cognitive domains, whereas healthy volunteers may be less able to benefit from higher ones (Linssen et al., 2014a).

There is accumulating evidence of an inverted U-shaped curve effect of dopaminergic drugs on task performance for a number of measures (Vijayraghavan et al., 2007; Levy, 2009; Clatworthy et al., 2009; Monte-Silva et al., 2009; Cools and D'Esposito, 2011; Berridge et al., 2012). For

example, MPH has been shown to cause a reduction in the go-trial reaction time in a stop-signal reaction time (SSRT) task (Eagle et al., 2007). In this study, its effects were relative to baseline performance: MPH decreased SSRT in slow responders but increased SSRT in fast responders – consistent with the "optimal DA" level / inverted U-shaped curve dose effects discussed in Chapter 1. Other task behaviours also demonstrate this effect: In a task testing visual short-term memory (vSTM), plasma levels of MPH were measured following 40mg oral administration. Higher plasma levels led to greater performance enhancement in low-performers and decreasing improvement in high-performers (Finke et al., 2010). Similarly, a study of dextro-amphetamine (AMP) found that stop-signal reaction time was improved only in those subjects with slow baseline stop RTs (de Wit et al., 2000). Alternatively, MPH may only exert it's effects upon those whose baseline performance is poor, as demonstrated in a recent study (Agay et al., 2014) and similar to the positive effects of L-dopa in PD. In fact MPH has already been demonstrated to improve response vigor in PD patients, but not healthy controls (Drijgers et al., 2012).

A possible mechanism for this individual difference in responding is implied by a radiolabelled (D2/D3 ligand $^{18}$F-fallypride) PET study (Volkow et al., 2002). This study found higher trait-impulsivity (BIS-11 score) was predicted by diminished D2/D3 autoreceptor binding and greater amphetamine-induced DA release in the striatum. Impulsive subjects might therefore be differently affected by the MPH than less impulsive ones. PET imaging has also demonstrated that therapeutic doses of MPH significantly increase extracellular DA in the basal ganglia but that this PET dopaminergic effect was affected by endogenous DA 'tone': MPH appeared to act through 'amplification' of each individual's baseline DA release rate (Volkow et al., 2002). This might also explain variability in individual responses to the drug.

Another explanation for lack of main effect could be differential dose responses. A study comparing the effects of MPH and atomoxetine upon the prefrontal cortex (PFC) of monkeys found an inverted-U dose response curve (Gamo et al., 2010). Optimal doses improved PFC function in a spatial working memory task, whereas excessive doses did not. These findings were mirrored by memory related neuronal firing, which was differentially blocked by both $\alpha$2 and D1 antagonists. A study of MPH dose-dependent effects upon 3 rhesus monkeys performing oculomotor delayed response tasks sensitive to working memory, impulsivity, response accuracy and precision as well as attentional performance found that task performance was affected in an inverted-U shaped manner with respect to dose (in all 3 monkeys) (Rajala et al., 2012): There was an initial reduction in premature responding but no benefit in remembering target locations. This effect declined with higher doses of MPH, as did performance on attentional measures. Significantly, there were task dissociable effects in that the optimal dose for "duration of participation" was already sufficient to impair working memory. This has connotations for clinical use, as well as for this study.

The inverted U-shape relationship between cognitive performance and dopaminergic activity in fronto-striatal circuits has also been investigated using radiolabelled neurotransmitter imaging (Clatworthy et al., 2009). [$^{11}$C]-raclopride radioligand PET imaging following a dose of 60mg MPH in healthy volunteers predicted performance on a reversal-learning task – specifically by

the drug-induced change in $D_2/D_3$ receptor availability in the post-commisural caudate. Spatial working memory task performance was related to similar changes in the ventral striatum. Interestingly, reversal-learning performance was also predicted by subjects' trait impulsivity (BIS-11): The most impulsive individuals (at baseline) benefited most from the drug.

The order of drug and placebo administration may also be important. In their study, Elliot *et al* (1997) found that although MPH *enhanced* spatial task performance when taken in the first session, it actually *impaired* performance accuracy when taken in the second session. Their explanation for this is that MPH might have a specific benefit on novel tasks, but otherwise impair previously established performance. We might have hoped that this would have been evident as a drug interaction with session order. However, the initial training session might have been sufficient to abolish any effect of MPH upon novelty. That being the case, we might have expected performance to be impaired by methylphenidate, but this also was not apparent.

We, and others, have focused on the possible dopaminergic effects of methylphenidate. However, it also has noradrenergic effects through reuptake inhibition. These effects may independently influence eye movement tasks. A visuo-motor control task found that the SNRI, reboxetine, caused both changes in dynamic causal modelling (DCM) and improved task performance (Grefkes et al., 2010). However, the output modality of this study was hand movement, so putative effects upon eye movements must be inferred with caution. Furthermore, dexmedetomidine, an $\alpha$2-adrenoreceptor agonist, had no effect upon saccadic latency, just saccade velocity (Aantaa, 1991).

### 6.4.3 Summary

Though both this experiment and that with levodopa (Chapter 5) failed to demonstrate significant effects of drug, there were interesting trends that may become significant on increasing the power of the study. Furthermore, stratification of larger groups through either genetic polymorphisms or baseline indices such as BIS-11 score could allow interrogation of differential effects on impulsive versus non-impulsive volunteers.

# 7. The Effects of Parkinson's Disease, Impulse Control Disorders and Pathological Gambling upon Oculomotor Impulsivity

## 7.1 Introduction

Why do some people take up gambling when for others it holds no interest? Some people feel compelled to gamble despite continued losses, leading them to financial (and social) ruin. In this extreme case the disorder is termed pathological gambling (PG) (Grant et al., 2014; Hinchliffe, 2014; Lobo et al., 2014). Such abnormal behaviour is associated with both impulsive traits and "novelty seeking" (Alessi and Petry, 2003; Blaszczynski et al., 1997; Fuentes et al., 2006; Michalczuk et al., 2011; Steel and Blaszczynski, 1998).

Parkinson's Disease (PD) is associated with both apathy (Starkstein et al., 1992; Isella et al., 2002; Pluck and Brown, 2002; Robert et al., 2002; Dujardin et al., 2007) and impulsivity (Nombela et al., 2014; Voon et al., 2011a; Weintraub and Nirenberg, 2012; Weintraub et al., 2010). In some PD patients, particularly those treated with dopamine agonists, impulse control disorders develop, including pathological gambling (Avanzi et al., 2006; Driver-Dunckley et al., 2003; Gallagher et al., 2007; Molina et al., 2000; Voon et al., 2011a; Weintraub et al., 2010). This propensity may reflect a gradient pattern of dorso-ventral striatal degeneration and/or differential dopaminergic treatment effects upon those structures (Steeves et al., 2009; MacDonald and Monchi, 2011; Lawrence et al., 2013).

Parkinson's Disease provides a model of disrupted fronto-striatal dopaminergic circuitry in which impulse control disorders (ICDs) may develop. This "PD-ICD" group can be compared with non-impulsive PD patients and gamblers without neurological disease as well as healthy volunteers. The Traffic Light Task (Chapter 2) encourages "functional impulsivity" (Dickman, 1990) through highly rewarded anticipatory eye movement behaviour. Would the impulsivity of known problem gamblers result in high rewards? Or, would gamblers be less sensitive to punishment and therefore persist in attempts to respond quickly, despite high rates of error (thereby exhibiting "dysfunctional impulsivity")? How might non-impulsive PD patients perform on the task and how would that contrast with PD patients with impulse control disorders? I used the Traffic Light Task and other measures to compare these groups with age-matched controls.

### 7.1.1 Disordered Decision-Making occurs in PD

Cognitive deficits are a recognised consequence of PD (Burn et al., 2014), including early in the disease course and younger patients (Aarsland et al., 2003; Collins, 1998; Lewis et al., 2003). Fronto-striatal executive impairment in non-demented PD patients may impair decision-making and/or change patients' risk sensitivity (Robbins and Cools, 2014). PD patients are less able to make profitable choices in the Iowa Gambling Task (IGT) compared with age and IQ matched healthy volunteers (Mimura et al., 2006). PD patients have also been found to be impaired on a Game of Dice Task (GDT), another measure of decision-making under risk (Brand et al., 2004). Some authors suggest that these IGT performance deficits emerge only *following treatment with dopamine agonists* and subsequent overstimulation of orbito-fronto-striatal networks (Poletti et al., 2010). In studying dopaminergic drug effects, investigators have found both 1) improvement in *some* cognitively demanding tasks and 2) impaired task performance in *other* kinds of test when comparing PD patients on and off medication (Cools et

al., 2003). In particular, it seems that dopaminergic medication *strengthens* associations between reward processing and novelty seeking but *disrupts* the links between punishment processing and harm avoidance (Bodi et al., 2009).

When reward processing and harm avoidance (and hence decision-making) are disrupted in PD, impulse control disorders may occur (Brand et al., 2004, 2005). PD patients with Impulse Control Disorders (ICD) seem to over-value immediate rewards despite intact reward learning (Housden et al., 2010). Would PD-ICD patients make excessive errors in the Traffic Light Task, driven by the desire for high rewards? Previous studies in patients with PD with and without ICDs inform our hypotheses about their oculomotor decision-making. A factor analysis (Poletti et al., 2010) comparing impulsiveness in PD patients (without *diagnosed* ICDs) with healthy, age-matched controls found that four principal factors explained 60% of the variance in the results (Nombela et al., 2014). Three of these four factors provide a useful framework for the consideration of experimental findings relevant to hypothesis formation for our battery of measures:

1. *Tests of response conflict, interference and self-assessment of impulsive behaviours on the Barratt Impulsivity Scale* (BIS-11, see Chapter 3).

A screen for ICDs, impulsivity and compulsive behaviours in a large cohort of PD patients *before* initiating dopamine replacement therapy showed that a significant proportion of PD patients did demonstrate ICDs. These patients had higher Attentional Impulsiveness (AI) compared to non-PD ICD subjects on the BIS-11 (Antonini et al., 2011). Results discussed in Chapter 3 suggest that higher AI scores might predict higher reward in both the Traffic Light Task (due to a higher AER) and the reverse traffic Light Task and greater reward *sensitivity* in the lateral reward task.

2. *Tests of motor inhibitory control, and the self-report behavioural approach system.*

An investigation of treated and untreated PD patients found higher "motor impulsiveness" and total BIS-11 scores in those with ICDs (Bentivoglio et al., 2013). There was also a trend toward worse performance of the PD-ICD group on neuropsychological tasks sensitive to frontal lobe dysfunction. We found no correlations between the motor and total BIS-11 scores and our oculomotor tasks (Chapter 3), however, we might speculate that our task is sensitive to frontal lobe dysfunction and that patients with PD-ICD might therefore perform more poorly than healthy controls.

3. *Time estimation and delay aversion*

Fronto-striatal systems appear to be important for shifting attention from one temporal context to the other (Meck and Benson, 2002). PD patients have been found deficient in estimating short (seconds) intervals but, by contrast, are equally capable of estimating longer (tens of seconds) intervals as controls (Riesen and Schnider, 2001). Their timing deficits appear to be ameliorated by dopaminergic treatment (Pastor et al., 1992; Lange et al., 1995; Malapani et al., 1998). Studies in the time range (hundreds of milliseconds) relevant to these experiments are few but have demonstrated sparing of this range while replicating the deficits found by others in the longer, "seconds", time range (Smith et al., 2007b). PD patients may therefore find oculomotor tasks,

which require an internal "representation" of time intervals for good performance (such as the Traffic Light and reverse traffic Light tasks), more difficult. However, the brevity of the task intervals used here (mean SRT delay 500ms, mean traffic light delay 750ms, Lateral Reward task delay 1000ms, mean reverse traffic light amber duration 1500ms) may render PD patients relatively unimpaired. If they *are* impaired, we might expect a restorative effect of dopaminergic medications upon their performance – perhaps such that levodopa equivalent dose (LED) correlates positively with task performance.

The fourth factor '*Reflection in hypothetical scenarios including temporal discounting'* is not directly relevant to our battery, but reaction time data from studies of temporal discounting may inform interpretation of our results: Increased temporal discounting and other treatment-related behavioural disorders occur in PD with PG (Voon et al., 2009; Housden et al., 2010). Patients in one of these studies had faster reaction times compared with PD controls (Voon et al., 2009). However, other authors found *no differences* in reaction times or error rates when PD patients with and without PG were compared on the Stroop test (Djamshidian et al., 2011; Rossi et al., 2010). As far as we know, no one has previously used saccadic (or other eye movement) tasks to compare Parkinson's patients with and without impulse control disorders.

### 7.1.2 Eye Movements in Parkinson's Disease Reflect Cognitive Processes

Numerous studies have demonstrated abnormal oculomotor control in PD (Jankovic, 2008). However, saccadic latencies appear to correlate with (diminished) executive function rather than motor severity (Perneczky et al., 2011), suggesting that they may remain useful for cognitive testing. Most relevant to The Traffic Light Task are PD effects on 1) simple reaction time, 2) antisaccades (a measure of prepotent response inhibition that is associated with impulsivity) and 3) anticipatory responding.

*Reflexive* saccades to visual targets are relatively spared from impairment in most reported studies of patients with PD (White et al., 1983; Rascol et al., 1989; Vidailhet et al., 1994; Briand et al., 1999). However there are exceptions to this, which demonstrate increased latency (Bronstein and Kennard, 1985; Shibasaki et al., 1979). In all the reported studies found using oculomotor prepotent response inhibition, latencies of antisaccades (AS) were increased and PD patients committed more pro-saccadic errors (Briand et al., 1999; Chan et al., 2005; Kitagawa et al., 1994; Lueck et al., 1990; White et al., 1983). In one of these studies, the latency increase correlated with the degree of bradykinesia (Kitagawa et al., 1994), suggesting that cognitive effects are not fully independent of motor severity.

With regard to the likelihood of anticipatory responding, PD patients have been shown to make more 'express saccades' (correct saccades in the latency range 90-140ms) in a study using both pro- and anti-saccades (Chan et al., 2005). However, an earlier study of PD patients and age-matched controls found that patients were *less* likely to make *anticipatory* saccades. This was thought to be due to their over-reliance on visual input (Bronstein and Kennard, 1985). In a study that used both manual and saccadic responses, the authors concluded that, though *capable* of predictive hand and eye movements, PD patients tend to avoid them due to their greater

inaccuracy (Crawford et al., 1989). We might therefore hypothesise that PD patients will commit more errors and/or avoid anticipation.

### 7.1.3 Pathological Gambling (PG) causes impaired prepotent response inhibition

To our knowledge, no one has previously used saccadic tasks to study problem gamblers. Furthermore, there is a lack of reports of fundamental psychophysical measures (such as a reaction time) in this group. Only seven specific neuropsychological experimental reports involving gamblers were found by a 2004 review (Goudriaan et al., 2004). This author has since described experiments which demonstrated that pathological gamblers performed poorly in tasks requiring inhibition, time estimation, cognitive flexibility and planning (Goudriaan et al., 2006a).

Gamblers also exhibit poor decision-making. Gamblers had impaired performance on three decision-making tasks and deficient feedback processing compared to the control group on the IGT and a Card Playing Task (Goudriaan et al., 2005). Delay discounting and decision-making impairment on the IGT are consistently found to be impaired in PG (Alessi and Petry, 2003; Cavedini et al., 2002; Kertzman et al., 2011; Petry, 2001).

Further behavioural investigation of pathological gamblers has focused on tasks of prepotent response *inhibition*, such as stop-signal reaction time (Lipszyc and Schachar, 2010) and Go/Nogo tasks (Kertzman et al., 2008): A (poorly controlled) study found that pathological gamblers' performance was impaired versus other groups in a stop-signal reaction time (SSRT) task (Odlaug et al., 2011). Gamblers also had slower response latencies on "go" trials and made more errors on a cognitive flexibility task. A major confound in this study was that of significantly higher chronological age in the pathological gambling group. This may account for some (or all) of the differences found. A better controlled study using both SSRT and delay-discounting tasks found greater delay discounting in all gamblers, but SSRT impairment only in the most severely affected (Brevers et al., 2012). A recent review found consistent abnormalities in pathological gamblers in the IGT, delay and probability discounting tasks but poor inter-task correlations (Wiehler and Peters, 2014). Genetic polymorphisms affecting genes encoding specific dopamine receptor subtypes have been associated with these task abnormalities (e.g. (Gray and MacKillop, 2014).

On the basis of these findings, we might hypothesise that pathological gamblers will be more variable in the their traffic light task responses and may fail to adapt their strategy to achieve optimum rewards.

### 7.1.4 Summary

Patients with Parkinson's disease demonstrate cognitive deficits in tasks sensitive to frontal lobe or executive dysfunction, including decision making tasks. Saccadic reaction times may be relatively spared but relate to cognitive deficits more strongly than motor impairment. There are similarities in the neuropsychological deficits of pathological gamblers. We investigated

these groups' performance in The Traffic Light Task, to further understand the effects of impulse control disorders on oculomotor impulsivity and to look for similarities and differences in the deficits shown by each group.

We investigated three patient groups:

1. Patients with Parkinson's disease (PD) without impulse control disorders (ICD)
2. Patients with Parkinson's disease with diagnosed ICDs (PD-ICD)
3. Problem gamblers *without* neurological disease (PG)
4. Age matched healthy volunteers

## 7.2 Methods

### 7.2.1 Experimental Groups

*PD Group*

Sixteen patients (8 female) with a diagnosis of idiopathic Parkinson's disease (PD) were recruited from general neurology clinics at the National Hospital for Neurology and Neurosurgery and Charing Cross Hospital. Fourteen of these (7 female, 2 left handed, mean age 64.8yrs, SD 8.2) went on to successfully complete 500 trials of The Traffic Light Task (Chapter 2) and the BIS-11 questionnaire (see Chapter 3). Two patients were taking no anti-Parkinsonian medication. The mean levodopa equivalent dose (using dose equivalencies according to (Tomlinson et al., 2010)) of all 14 patients (L-dopa Equivalent Units, LEU) was 308mg/day (SD 362) of which a mean of 113mg/day (SD 110) were due to DA agonists. The patients' mean Unified Parkinson's Disease Rating Scale (UPDRS) was 31 (SD 11).

Two patients failed to complete the task due to one being unable to learn the task and one because of impaired vision/technical failure of eye tracking due to spectacles. Some of the 14 participants completed newer tasks described elsewhere in this thesis. Though they are not the main subjects of this chapter, the results of the other tasks will be presented here, where informative.

*PD-ICD Group*

Seven patients (1 female, mean age 50yrs, SD 11yrs, 1 left handed) with a diagnosis of Parkinson's disease who had developed and been diagnosed with an impulse control disorder *since diagnosis* were recruited and tested. Patients with identified impulse control disorders, a prior history of gambling, alcoholism or other addiction were excluded. These patients were identified by their participation in other research at the Institute of Neurology, University College London.

The patients had a heterogeneous group of ICDs: One patient collected compulsively (O'Sullivan et al., 2010a), one was recklessly generous (O'Sullivan et al., 2010b), one was adulterous and four had developed pathological gambling. The extent of the gambling ranged in severity from a significant increase from baseline (pre-Parkinson's) gambling to severe pathological gambling leading to bankruptcy.

All 7 ICD-PD patients were taking anti-Parkinsonian medication. The mean LEU dose of was 478mg/day (SD 379) of which a mean of 144mg/day (SD 145) were due to DA agonists. Both mean LEU and LEU due to DA agonists were therefore (non-significantly) higher than in the PD without ICD group. The patients' mean Unified Parkinson's Disease Rating Scale (UPDRS) was also non-significantly higher than in the non-ICD group (mean 57, SD 21).

Tasks presented: All PD-ICD subjects completed the SRT task (Chapter 2), the Traffic Light Task (Chapter 2), The Lateral Reward Task (Chapter 3) and The Reverse Traffic Light Task (Chapter 3).

*PG Group*

11 gamblers (all male, all R handed, mean age = 37.0 yrs) were recruited from the National Problem Gambling Clinic in Soho (Central and North West London NHS Trust) after identification as suitable following a review of the medical records. Comorbid psychiatric disorders or neurological disease were exclusion criteria. Gamblers were at various stages of assessment and/or treatment for problem gambling as identified by their G.P. or by self-referral.

Tasks presented: 10 gamblers completed the SRT task, the traffic light task, the lateral reward task and the reverse traffic light task. The 11th subject performed the SRT and traffic lights tasks only. 8 completed the BIS-11, the other 3 refused.

*Controls*

Age matched controls for the PD group (Older volunteers, n=14, 8 female, 3 left handed, mean age 65.5yrs, SD 8.9) were drawn from our older healthy volunteer group (see Chapter 2). Older volunteers completed the BIS-11 and traffic light task only.

Due to difficulty in recruiting healthy volunteers in the 50 to 65 year age group (particularly male) for comparison with the PD-ICD and PG groups, controls for SRT, Reverse Traffic Light and Lateral reward tasks were necessarily younger than the patient group. This group is referred to as Middle 1.

A second, better age matched group drawn from both the older control group and the middle aged control group was used as a control set for the traffic light task. This group is referred to as Middle 2.

Middle 1: Controls (n=13, all male, 3 left handed, mean age 41, SD 5.7) were drawn from our healthy volunteer group.

Middle 2: Controls (n=16, 5 female, 3 left handed, mean age 50, SD 10.7) were drawn from our healthy volunteer group.

### 7.2.2 The Barratt Impulsiveness Scale (BIS-11)

The 30-item BIS-11 questionnaire (Patton et al., 1995; Stanford et al., 2009) measures impulsiveness through items such as "I act on impulse" and "I consider myself always careful". Participants indicate how frequently each statement applies to them on a 4-point Likert scale (*never*, *occasionally*, *often*, and *almost always*). Possible score totals range from 30 to 120, with higher scores indicating greater total levels of impulsiveness. Analysis of the BIS-11 comprises six first-order factors: attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability. These first-order factors are combined to generate three second-order factors: attentional impulsiveness (inability to focus attention or concentrate), motor impulsiveness (acting without thinking), and non-planning impulsiveness (lack of forethought).

### 7.2.3 Oculomotor Tasks

*Oculomotor Task Apparatus and Data Acquisition*

Subjects sat on a height adjustable chair under a height adjustable table in a dimly lit room. They placed their forehead on a rack mounted EyeLink 1000 infra-red video-based eye tracker (SR Research Ltd, Ontario, Canada) recording eye position at 1000 Hz. A chin rest was then adjusted to provide comfortable support. The task stimuli were displayed on a flat screened 22" CRT monitor (Dell P1230, 507.7mm viewable, displaying 1024x768 pixels, refresh rate 150 Hz) at 60cm from the vertical plane of the subject's eye. Eye position was calibrated to a 9 point rectangular matrix before testing began.

The task stimuli were programmed in C/C++ and run on a personal computer ((PC), Dell Optiplex 755 running Windows XP SP3). The eye tracker was controlled by a separate PC (Dell Precision 380) networked to the stimulus/display PC. This allowed real-time task feed-back responses to eye movements. Eye position and pupil area data were acquired in real time and exported into Matlab R2008a (The Mathworks, Massachusetts, USA) for analysis.

*Data Analysis*

Eye position data was used to detect fixations during each trial. Though blink errors were unavoidably included in the real-time feedback to the participant, blink trials were excluded from our *post hoc* analysis.

#### 7.2.3.1 Traffic Light Task (See Chapter 2 & Figure 2.1)

In the Traffic Light Task, participants were told that their main aim was to win *as much money as possible*. They were asked to make rapid eye movements from a 'traffic light' (coloured disc 3 degrees in diameter) to a target cross (3x3 degrees), both presented on a computer monitor (60cm from the chin rest/plane of the eye). The traffic light and target were 10 degrees either side of the screen center. Subjects were requested to fixate the traffic light stimulus while it turned from red (duration 1000 ms) through amber to green. They were asked to make their 20 degree saccade to the target cross *as quickly as possible* and as soon after the GO signal as possible. They had a maximum of 1000ms in which to respond.

The reward ($R$) for a successful saccade was calculated by an exponentially decaying discounting function in the form:

$$R = ae^{-\left(\frac{t-t_0}{k_1}\right)}$$

Where $a$ = 150, $k_1$=100 and $t$ represents the saccade onset time relative to green onset ($t_0$, milliseconds).

The timing of the GO signal (green light) onset was not absolutely predictable from trial to trial. Instead, the duration of the amber light (Figure 2.1B) was randomly selected on each trial from a normal distribution (mean 750ms, SD 125ms). To perform optimally, participants therefore needed to make as many rewarded anticipations as possible, while keeping errors to a minimum. They had to make a choice of whether to stay (wait longer) or go and risk a small penalty versus the possibility of a large reward. On gaze arriving at the target cross (fixation tolerance 2°), subjects received both aural and visual feedback on their performance. They were shown the reward (in pence) on the trial just completed, and a running total beneath (in pounds). There were also aural cues to trial performance. For rewards of less than 20 pence, they heard a 'ping'. For rewards of 20 pence or more, they heard a more rewarding 'kerching!' sound. The target cross was then replaced by a red light (circle) and a target cross now appeared on the opposite side of the screen to begin the next trial. To perform optimally, subjects should therefore make as many anticipations as possible, but as few errors as possible. Subjects performed ten blocks of fifty trials, the first trial in each block started from a left sided stimulus (rightward saccade) and then alternated.

#### 7.2.3.2 Saccadic reaction time (SRT) task (See Chapter 2 & Figure 2.2)

In addition to The Traffic Light Task, some subjects were also tested on a control, non-rewarded saccadic reaction time (SRT) task. In this paradigm, the red light was followed immediately by green, with no amber light between these. Red light duration varied between 500-1000ms (rectangular probability distribution, mean 750ms). Data acquisition was as above. This task allowed us to obtain response distributions for 'reactive' saccades – those programmed in response to green onset, without any need to anticipate the GO signal.

#### 7.2.3.3 The Lateral Reward Task (See Chapter 3)

Subjects were asked to fixate a central spot for 1000ms before making a saccade to a target appearing 10 degrees to the right or left (50% probability on each trial). The rewarded side changed every 10-14 trials, jittered such that 60 leftward and 60 rightward rewarded sides were encountered by each subject overall, in a 120 trial block. Rewarded trials were acknowledged by the display of a pound coin and a number representing the magnitude of the reward in pence. Reward value was dependent on latency using a similar function to that employed in the Traffic Light Task. The reward function was slightly shifted to accommodate longer mean latencies (discovered in piloting) due to the unpredictable target position. A red circle and a zero acknowledged unrewarded trials.

Participants performed two blocks of 120 trials. Their reward for participation was scaled to their total reward accrued across the tasks presented. The difference between the reaction times to the rewarded and unrewarded sides was used as a measure of a subject's sensitivity to reward.

#### 7.2.3.4 The Reverse Traffic Light Task

In this task, patients were told to fixate a green light that would then turn amber (after 1000ms). They were told to make their saccade at some time during the amber light. It was explained that the later they made their eye movement, the more highly rewarded their response would be. However, were the amber light to turn red before they made their eye movement, they lost 10 pence. The amber light duration was varied randomly from trial to trial selected at random from a Gaussian probability distribution with a mean of 1500ms (SD 500ms). This was intended to force subjects to wait slightly longer on each trial than in the traffic light task and also to avoid "cross-over" effects between tasks, within or across testing sessions.

$$R = Ae^{(ts-t\alpha-t\Omega)/t\Omega \bullet \kappa}$$

*R=reward (in pence), A=150, $t_s$ = time of saccade, $t_a$ = time of amber onset, $t_\Omega$ = time of red light onset, $\kappa$=0.1*

The closer subjects make their saccade to the red light onset, the greater the reward they received. Due to the changing amber duration, the reward calculation had to be slightly more complex: Reward was derived as an exponentially increasing figure related to the red onset on each trial. The reward curve is "fitted" into the variable amber duration on each trial. There is, therefore, not a fixed reward for any particular anticipatory gap, however this contingency ensures that similarly high rewards are achieved for accuracy on each trial.

Performance on this task was measured both in terms of reward accrued and in terms of the mean Stop Anticipatory Interval (SAI), the mean amount of time between subjects' saccades and the programmed onset of the red light.

## 7.3 Results

### 7.3.1 BIS-11

The PD group mean total BIS-11 score was 61.3 (SD 9.3) (See Table 7.1). The older volunteers mean was 59.5 (SD 10.8). These were not significantly different. Neither did patients nor age-matched controls differ significantly on any factor or dimension of the BIS-11 {Attention, Motor, Self-Control, Cognitive Complexity, Perseverance, Cognitive Instability, Attentional Impulsiveness, Motor Impulsiveness, Non-Planning Impulsiveness }.

PD-ICD patients were non-significantly more impulsive than controls according to BIS-11 totals. The mean PD-ICD total was 67.0 (SD 11). One patient (Subject E) who continued to use DA agonists despite on-going gambling problems scored 88 on the BIS-11. The Middle 1 group

scored a mean of 65.4 (SD 12.9). The Middle 2 group scored a mean of 61.8 (SD 12.8). These were not significantly different from any other group.

As expected, the pathological gamblers (PG) group were significantly more impulsive compared to both age matched control groups: $BIS\text{-}11_{(Gamblers)}$ mean = 75.56, SD 10.1, $BIS\text{-}11_{(Middle1)}$ mean = 65.4, SD 12.9, 1-Tailed Student's T test: $t(18) = -1.95$, $p=0.03$; $BIS\text{-}11_{(Middle2)}$ mean = 61.8 SD, 13.2, 1-Tailed Student's T test: $t(22) = -2.52$, $p=0.02$).

| *Bis-11 totals* | *Males* | | *Females* | | **Whole Group** | |
|---|---|---|---|---|---|---|
| *Group* | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* |
| **Middle Aged Controls (All)** (m11;f3) | 65.82* | 12.60 | 64.33 | 11.02 | 65.50 | 11.88 |
| **Middle 1** (m13;f0) | 65.40 | 12.90 | - | - | 65.40 | 12.90 |
| **Middle 2** (m11;f5) | - | - | - | - | 61.80 | 12.8 |
| **Elderly Controls** (m5;f12) | 57.40 | 11.48 | 60.33 | 10.88 | 59.47 | 10.78 |
| **PD Patients** (m6, f6) | 63.33 | 10.58 | 59.33 | 8.33 | 61.33 | 9.32 |
| **PD-ICD Patients** (m6;f1) | 69.17 | 11.32 | 56 | - | 67.29 | 11.47 |
| **Pathological Gamblers** (m11;f0) | 75.56* | 10.10 | - | - | - | - |

## Table 7.1 Mean BIS-11 Scores for each group

Pathological gamblers were significantly more impulsive than age-matched controls (*Student T-test, 1 tailed, $t(17) = 1.89$, $p<0.05$)). All other meaningful group comparisons (including between genders within groups) found no statistically significant differences.

### 7.3.2 SRT Task

5 PD patients completed the SRT task. Their mean saccade latency was 537ms (mean SD 148ms). Their responses formed a typical recinormal distribution (Figure 7.1). The SRT task was developed after older, age matched, controls were tested. We do not therefore have age matched control group for this task. The PD patients were significantly slower and more variable than middle-aged volunteers (mean 411ms, SD 56ms; 2-tailed Student T-test, $t(16)=2.72$, $p=0.02$). However, an *F*-test found the two samples to be of significantly different variances ($F(4,12)=6.75$. $p=0.02$). A Welch's T-test (for samples of unequal variance) does not reach the required significance level ($t(4)=1.87$, $p=0.06$).

All seven PD-ICD patients completed the SRT task. Their mean SRT was 442ms, SD 91ms. Variability was therefore intermediate between controls and non-ICD PD patients. A recinormal distribution was produced by the task (Figure 7.1). There was no significant difference between the PD-ICD patients and controls, neither did an *F*-test find the samples to differ significantly in variance.

The mean of gamblers mean latencies in the SRT task was 438ms (mean SD 128ms). The task generated a recinormal distribution of responses (Figure 7.1). There was no significant difference when compared to the age matched control group. However, the greater variability in the gamblers was reflected in a significant *F*-test demonstrating the two samples to be of different variance ($F(10,12)=4.01$, $p=0.01$).

In summary, the PD, PD-ICD and PG group were all more variable in their responding than controls, but this effect was only statistically significant for the PD and PG groups. Though PD patients were slower, they were also the most variable, and were older than the control group.

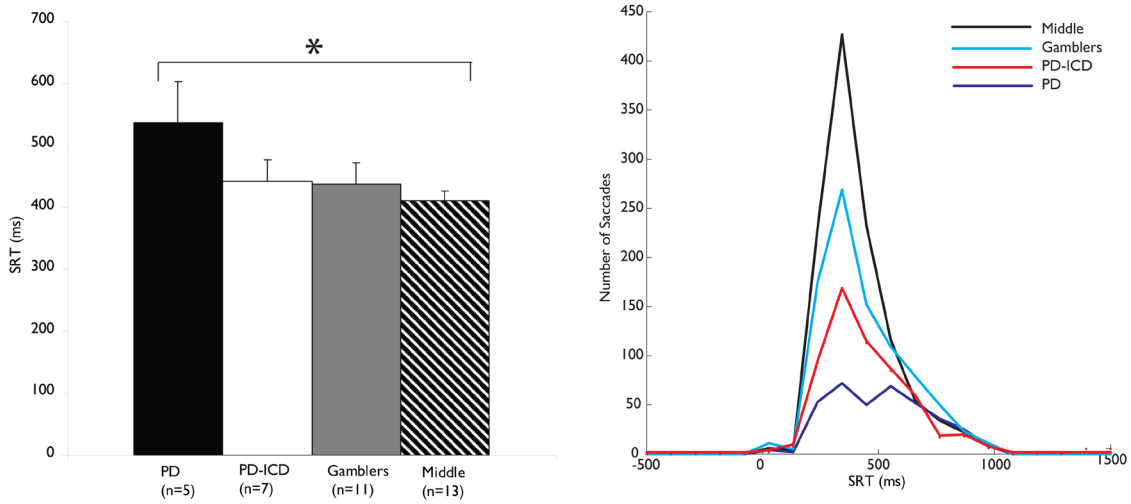



**Figure 7.1 SRT Task performances across groups**

Saccadic latencies are significantly slower comparing PD patients and a group of middle-aged healthy volunteers. The PD group were also significantly more variable in their responding. Both PD-ICD and PG groups were also more variable than controls, the PG group significantly so. There were no significant differences in reaction time between these groups, however. All groups produced a recinormal distribution of saccadic latencies.

### 7.3.3 The Traffic Light Task

*PD Group*

PD patients demonstrated little anticipation in the traffic light task (Figures 7.2 & 7.3). One patient made no anticipatory saccades (Subject J). Subject C made the greatest number of correct anticipations, making 116 such saccades (25% of non-blink trials). This range is similar to that seen in age-matched controls (min 0 [n=3], max 127 (32%) anticipatory saccades, Figure 7.3). Of the 14 PD subjects, only 5 demonstrate a convincing bimodal distribution of saccadic responses (Figure 7.2).

The low rate of anticipation (mean 7.0% of trials, SD 8.5%) led to a modest mean reward per trial (mean 7.1p, SD 4.1p, Figure 7.3). As expected, PD patients accrued *even less* reward than age-matched controls (mean 9.7p, SD 3.9p, 1-tailed Student T-test, $t(26) = -1.71$, $p<0.05$). This was not due to the anticipatory rate. In fact, the mean number of anticipations (saccades of latency 0-200ms) was similar identical (PD 7.0% of trials, SD 8.5%; Older 6.0% of trials, SD 9.9%). However PD patients did make non-significantly more errors (saccades before the green "Go!" signal; PD 13.5% of trials, SD 10.6%; Older 8.4% of trials, SD 10.7%). The PD correct Anticipations:Errors ratio (AER) was therefore non-significantly lower (0.42, SD 0.34) than that of the controls (0.70, SD 1.16). The main feature was the large range in this data for both groups, for example 0-116 anticipations by PD patients and 0-127 anticipations by older controls (three of whom made zero anticipatory responses).

Since there were no age-matched controls for the SRT task, it is useful to separately consider the reactive saccades (those made at >200ms latency). The mean latency for these in the PD patients was 379ms (SD 62.4ms) compared to the control mean of 350ms (SD 68.0ms). Though this difference was also not significant, the combination of greater errors in the early distribution and a longer latency for the reactive distribution combine to explain the significant reward reduction in PD patients.

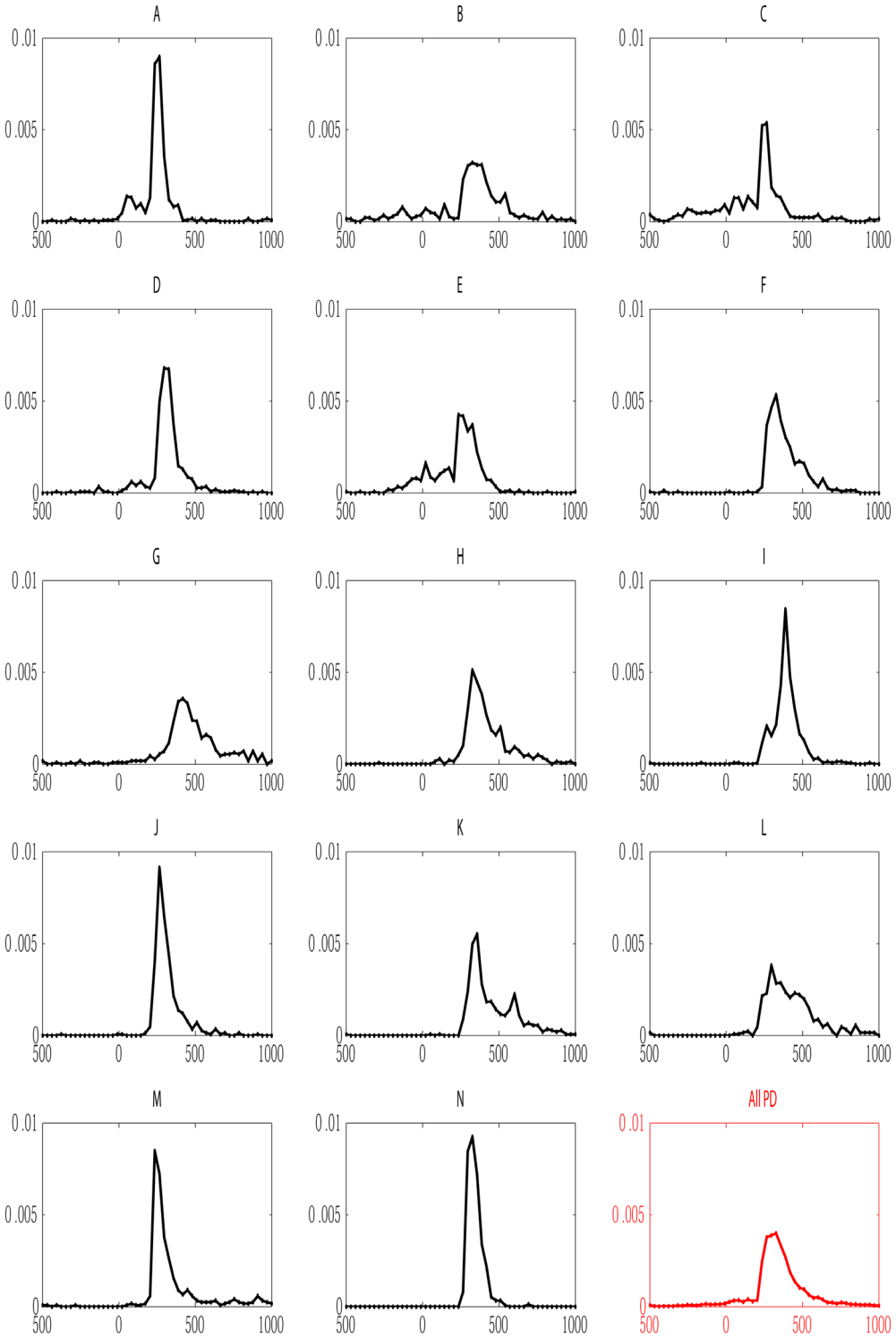



**Figure 7.2 PD Probability densities for saccadic latencies in the Traffic Light task:**

14 PD Patients (Subjects A:N) and the group as a whole. X axes: Response latency (milliseconds), Y axes: Probability Density (no units).

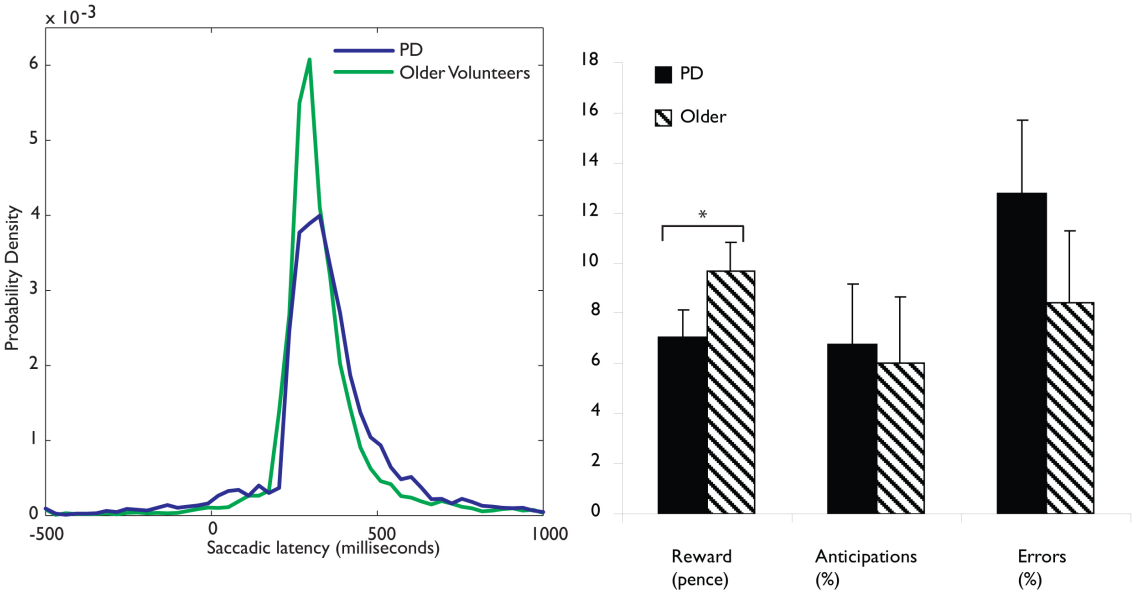



**Figure 7.3 Traffic Light Saccade Distributions and Performance Analysis.**

Both PD patients and Older Volunteers show very few anticipatory saccades leading to near unimodal saccadic distribution (left), with only a very small early distribution of saccades. However, there is a significant difference in reward benefitting the healthy controls. Separate analysis of the number of correct and anticipations (right) reveals that this is due to a slightly greater rate of earlier, mostly erroneous, responding overall in the PD group. Within the PD early responses, there are a greater number of errors relative to correct anticipations (neither result is statistically significant). The PD reactive distribution is also (non-significantly) right-shifted (of longer mean latency) compared to the controls.

*PD-ICD Group*

PD-ICD patients show some anticipation in the traffic light task (Figures 7.4 & 7.5). There is more evidence of a bimodal distribution than was evident for older PD patients and controls. There is an early distribution of responses that begins before the "Go!" signal but that also includes many highly rewarded saccades in the 0-100ms range. This is similar to the response of the age-matched controls.

The moderate rate of anticipation (mean 13.9% of trials, SD 12.9%) led to a moderate mean reward per trial (mean 8.5p, SD 5.2p, Figure 7.5). PD-ICD patients accrued less reward than age-matched controls (mean 12.8p, SD 5.8p, n.s.). This was due to the lower anticipatory rate (Middle 2 mean 15.7% of trials, SD 12.9%, not significant) and a similar error rate to controls (PD-ICD mean 24.4% of trials, SD 8.3% ; Middle 2 mean 24.2%, SD 21.1%). The PD-ICD Anticipations:Errors ratio (AER) was therefore non-significantly lower (0.49, SD 0.4 ) than that of the controls (0.76, SD 0.67 ).

PG Group

The majority of the pathological gamblers' (n=11) traffic light saccade distributions (Figures 7.6 & 7.7) demonstrate a bimodal distribution of early and reactive responses. Only one subject (subject K) shows very little anticipation.

Performance on the task was good, with a group mean reward per trial of 15.4p (SD 30.4p). This was non-significantly less than age matched healthy controls without gambling problems (n=13, mean reward 17.6p, SD 31.4p). This was due to a trend toward fewer correct, highly rewarded, anticipations in the gamblers (mean 21.0% of trials, SD 10.1%) than in the control group (mean 24.5% of trials, SD 8.0%) and the gamblers also committed a non-significantly greater number of errors (mean 27.3% of trials, SD8.0%) compared to controls (mean 24.2% of trials, SD 12.6%). This trend would appear to indicate a slight leftward shift in the early distribution of saccades. If we isolate responses made at <200ms, this is demonstrated by a non-significantly lower mean anticipatory latency of 92.8ms (SD 19.9ms) versus 101ms (SD 10.8ms) in the controls.

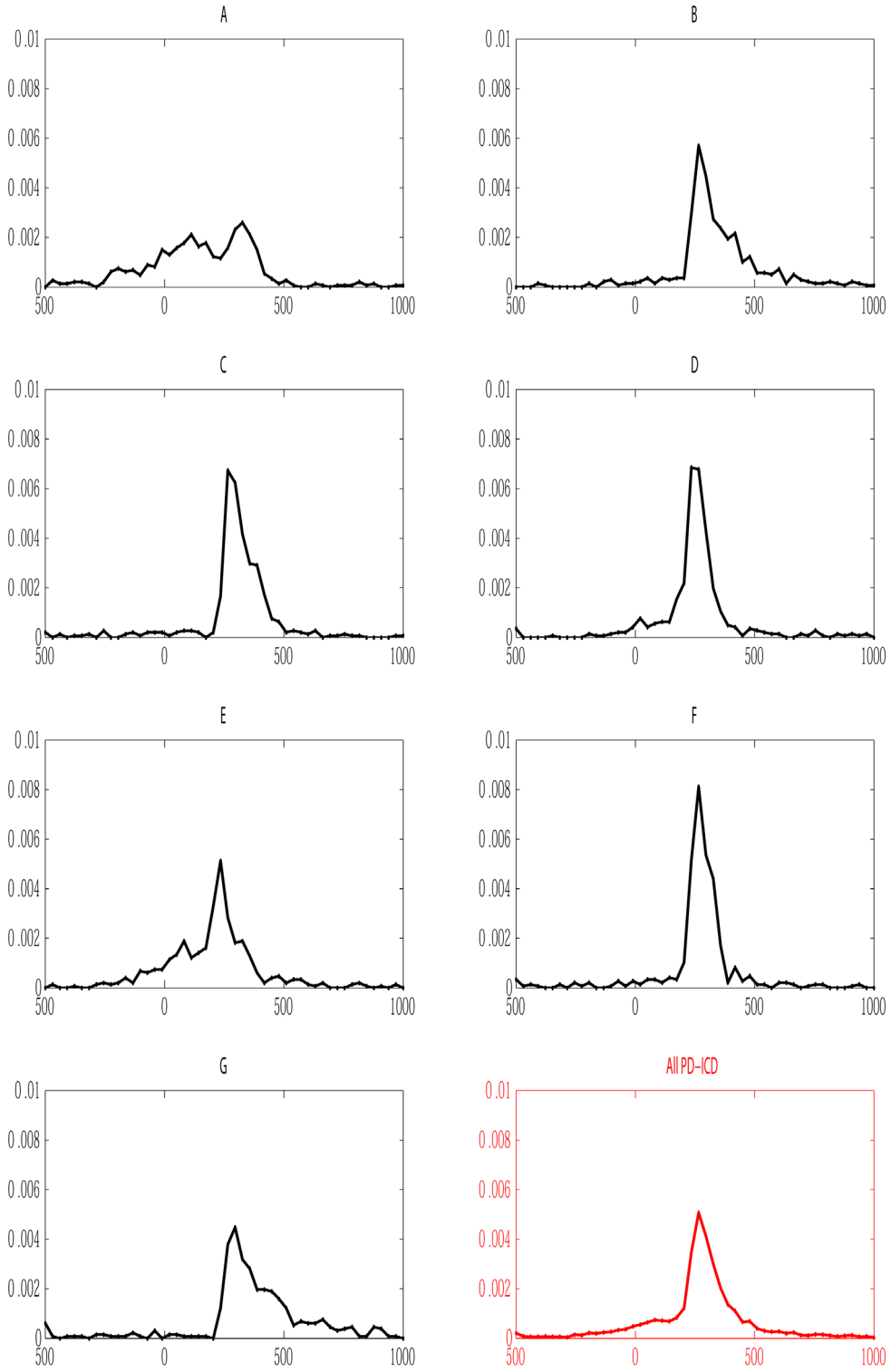



**Figure 7.4 PD-ICD Probability densities for saccadic latencies in the Traffic Light task**

7 PD-ICD Patients (Subjects A:G) and the group as a whole. X axes: Response latency (milliseconds), Y axes: Probability Density (no units)

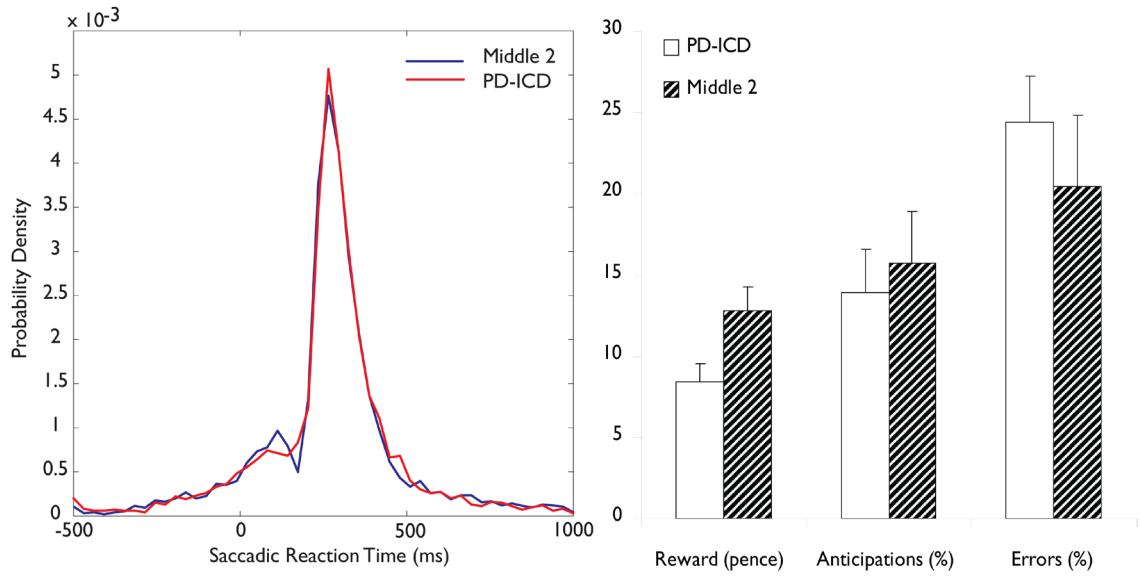



**Figure 7.5 PD-ICD Saccade distributions in response to the Traffic Light Task**

The PD-ICD population does make anticipatory saccades - non- significantly fewer than age-matched controls. They also make non-significantly more errors than controls. The result of these effects is a non-significant reduction in reward.

Reactive saccades (responses >200ms), on the other hand, are slightly right shifted (mean 346ms [SD 40ms] compared to 327ms [SD 58ms] in controls). Reactive saccades are more variable (mean SD 163ms compared to 132ms in controls). F-tests show that this difference is also not statistically non-significant, but the combination of a left shifted (more erroneous) early distribution, a right shifted (slower) reactive distribution and greater response variability explains the reduction in overall reward.

*Age Effects*

As discussed in Chapter 2, healthy volunteers produce fewer anticipatory responses as they age. Pathological gamblers were the youngest study group here, followed by the PD-ICD group and the PD group who were oldest. Plotting the response distributions compared to control groups of similar ages reveals quite similar differences. This suggests that any disease or condition specific differences may be being masked by a larger age-effect (Figure 7.8).

*Traffic Light Task Performance Indicators*

There is a strong correlation between the ratio of correct anticipations to erroneously early responses (AER) and reward (Figure 7.9). AER was found to correlate with both BIS-11 factors and other oculomotor task performance indicators in the experiments reported in Chapter 3. The gamblers make many early responses, however, they make so many errors that the AER is similar to that of older controls, who make few early responses. However, the task strongly rewards early responding (due to the steeply declining reward/latency curve), so gamblers nevertheless outperform older controls in terms of reward.

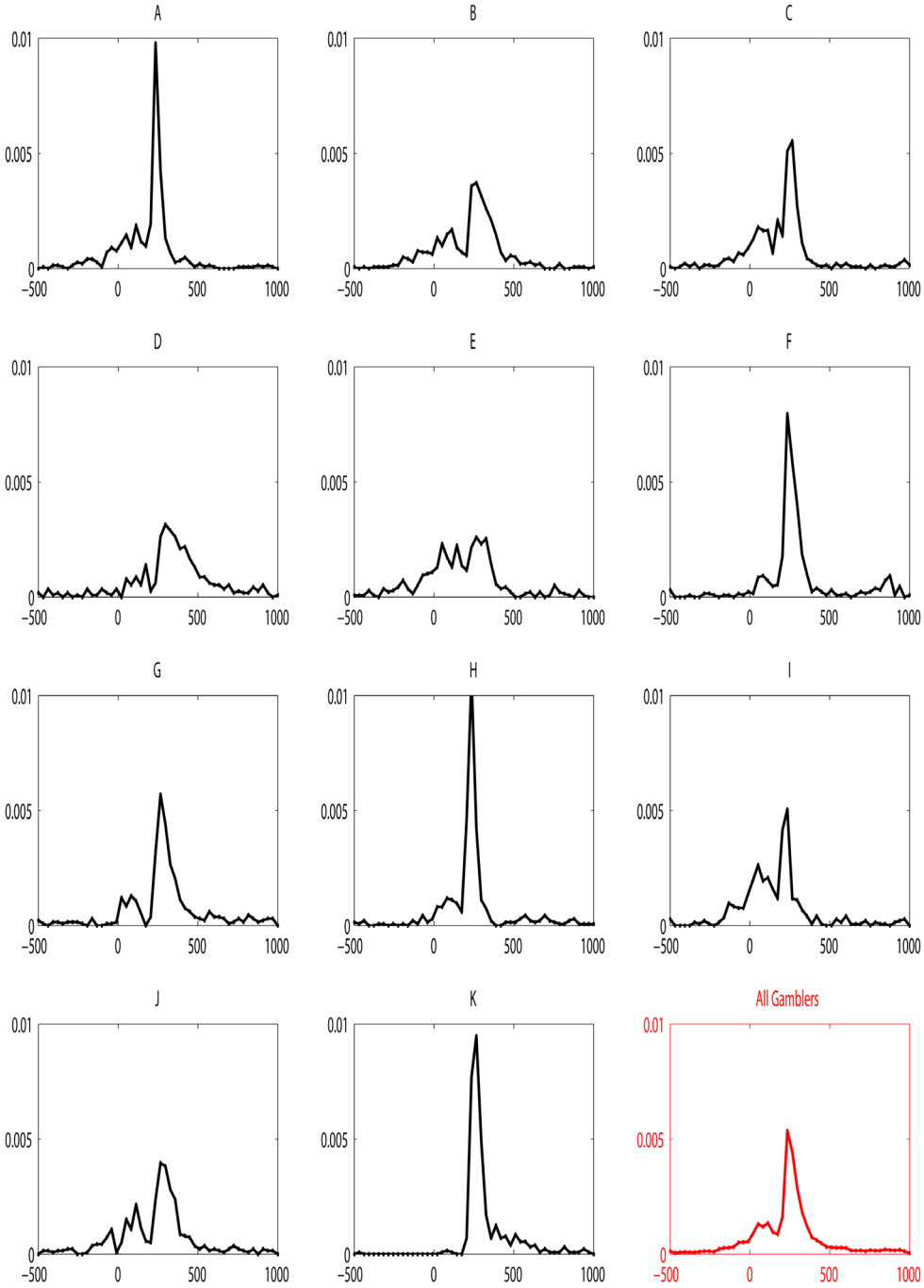



**Figure 7.6 PG Probability densities for saccadic latencies in the Traffic Light task**

11 Gamblers (Subjects A:K) and the group as a whole. X axes: Response latency (milliseconds), Y axes: Probability Density (no units)

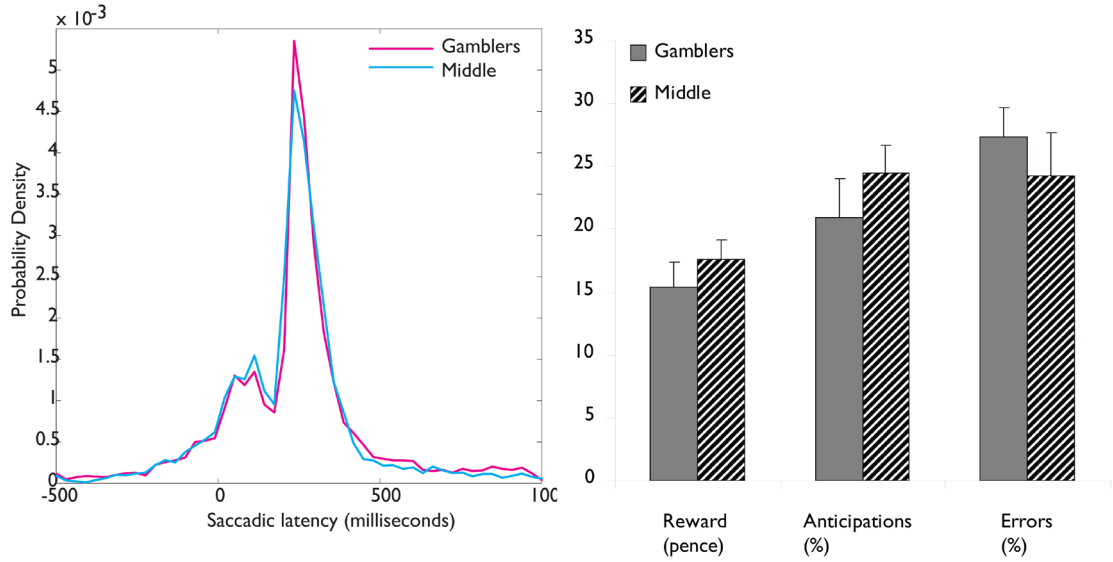



**Figure 7.7 Saccade distributions for Gamblers compared to age-matched controls on the traffic Light Task.**

The response distributions are very similar and the subtle differences in numbers of errors and correct anticipations within the earlier distribution are not easily perceptible. There are no significant differences between reward, anticipations and errors when comparing means. However, there is a general trend toward lower rewards as a consequence of fewer correct anticipations and more errors.

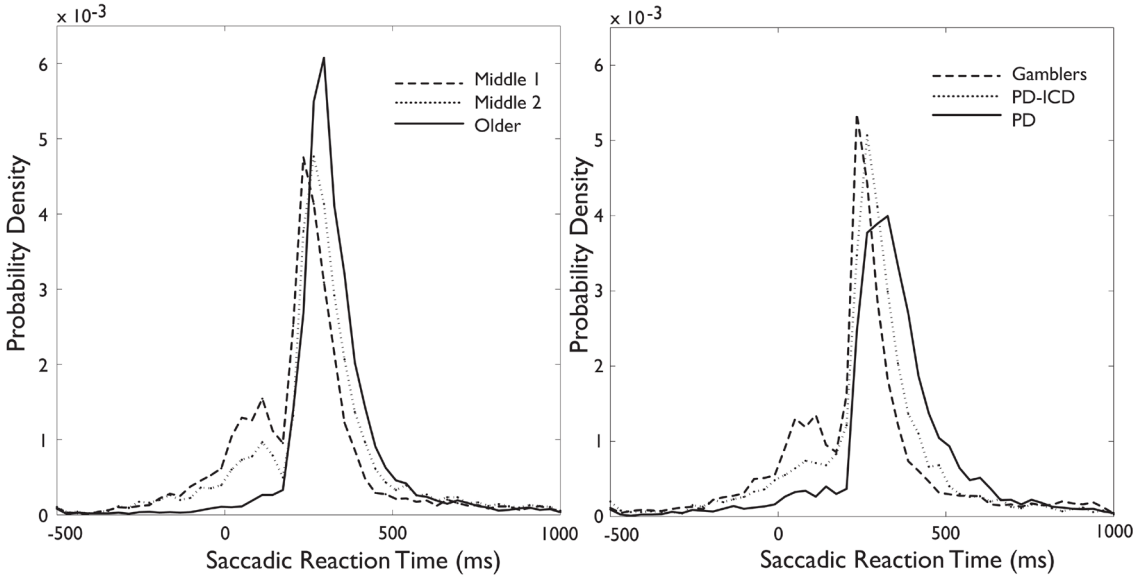



**Figure 7.8 Traffic Light Response Distributions – Age & Disease Effects**

The saccade distributions from the traffic light task reveal differences between both healthy volunteers from different age groups and between the experimental groups {PD, PD-ICD, Gamblers} described in this chapter.

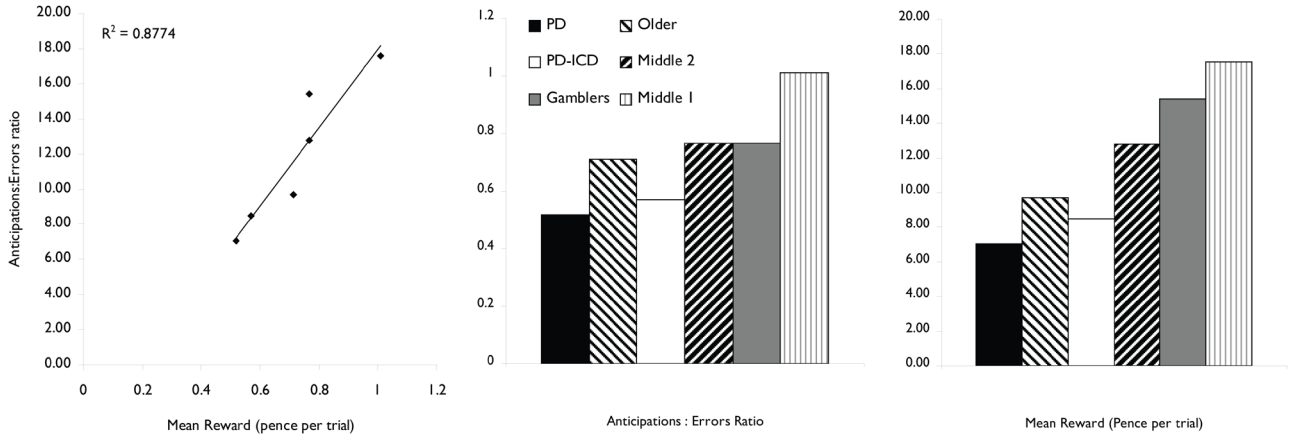



**Figure 7.9 Traffic Light Task Performance**

There is a strong correlation between the ratio of correct anticipations to erroneously early responses and reward. Gamblers make many early responses, however, they make so many errors that the ratio is similar to that of older controls, who make few early responses. However, the task strongly rewards early responding (due to the steeply declining reward/latency curve), so gamblers nevertheless outperform older controls in terms of reward.

### 7.3.4 Lateral reward

3 of the PD patients completed the lateral reward task. None showed significant speeding toward rewarded targets. Furthermore, two of the patients were *slower* to rewarded targets than unrewarded, (though neither difference was statistically significant).

Six PD-ICD patients completed the lateral reward task. There was no statistically significant difference in group means but a trend toward slower saccades to unrewarded targets (LRU = 292ms, SD 56ms) compared to rewarded targets (LRR = 284ms, SD 59ms). Two of the six individuals showed significant speeding toward rewarded targets. (Subject B mean LRU = 248ms, SD 64ms; LRR = 230ms, SD 58ms; 1-tailed Student T-test 191ms, $t(238) = 2.27$, $p=0.01$. Subject D mean LRU = 191ms, SD 27ms; LRR = 185ms, SD 24ms; 1-tailed Student T-test 191ms, $t(238) = 1.66$, $p=0.048$).

By contrast, the PG group showed significant reward sensitivity in the lateral reward task. There was speeding toward rewarded targets (Group mean LRU =242ms, SD 26ms; mean LRR = 217ms, SD 27ms; 1-tailed Student T-test $t(18) = 2.07$, $p=0.027$).

In the (larger n=13, Middle 1) control group, no overall significant group effect is seen but there is a trend toward speeding (Mean LRU = 235ms, SD 15ms, Mean LRR = 231ms, SD 17ms). 2 individuals showed statistically significant speeding (Subject B mean LRU = 248ms, SD 64ms; LRR = 230ms, SD 58ms; 1-tailed Student T-test 191ms, $t(238) = 2.27$, $p=0.01$. Subject D mean LRU = 191ms, SD 27ms; LRR = 185ms, SD 24ms; 1-tailed Student T-test 191ms, $t(238) = 1.66$, $p=0.048$) and the remaining subjects show a trend to shorter latencies for the rewarded side.

These results suggest that PD patients might have reduced reward sensitivity whereas pathological gamblers reward sensitivity is heightened.

### 7.3.5 Reverse Traffic Lights

PD patients did not perform the reverse traffic light task.

3 PD-ICD patients attempted the reverse task. Of these only 2 completed all 100 trials. Nevertheless, the mean Stop Anticipation Interval (SAI, 339ms, SD 57ms) and mean reward per trial (13.8p, SD 3p) for these two patients were similar to those seen in the control group (n=8, mean SAI 393ms, SD 89ms; mean reward 9.15p, SD 3p)). The task was later abandoned for use in impulsive patients as they generally found it too difficult to tolerate the prolonged fixations required.

The mean anticipation of the stop signal by gamblers (n=10) in the reverse task was 412ms (SD 77ms) yielding a mean reward of 10.6p per trial (SD 2.9p). This was similar to the performance of age-matched controls.

### 7.3.6 Levodopa equivalent dose (LED) & disease severity

There were no significant correlations between individual LED or UPDRS values and any outcome parameters. The PD-ICD group had a non-significantly greater mean LED and UPDRS score than the PD group. Normal reward performance in the PD-ICD group may be due to greater dopaminergic medication dosages (possibly leading to restoration of reward sensitivity and reduction in saccadic latency). The lack of correlation between task performance and motor severity is also consistent with previous studies of saccadic latency.

## 7.4 Discussion

### 7.4.1 Summary of findings

*BIS-11*

There were no significant differences in BIS score between PD patients and age-matched controls. The group size of PD-ICD patients was small, which limited the power of the study, however there was a trend toward higher BIS-11 scores, as has been found by previous investigators (Antonini et al., 2011; Bentivoglio et al., 2013). Pathological gamblers were significantly more impulsive according to BIS-11 scores, as expected and found in previous studies (Martins et al., 2004).

*Traffic Light task*

In the main Traffic Light Task, PD patients made significantly less reward than healthy, age-matched controls. This was due to a combination of a greater number of errors, fewer correct anticipations and slower reactive saccades. Responses in the SRT task were also slow and highly variable. Anticipatory responses in the Traffic Light Task were non-significantly greater in number than controls. This suggests that PD patients continued to make early responses despite higher error rates, and therefore failed to learn from negative feedback. This is a feature of other studies of reward learning in PD where intact learning from positive feedback is seen but there is a lack of response to negative feedback, or aversive learning (Cools, 2006; Rowe et al., 2008).

PD-ICD patients were similar in their rate of anticipation to age-matched controls, but there was a trend toward fewer rather than more correct anticipatory responses, in contrast to the PD group. This may suggest greater fronto-striatal dysfunction in the PD group compared to PD-ICD (Santangelo et al., 2009), however, the PD-ICD group were also younger, so it is not possible to separate the contributions of age and impulsivity in this study. This result is consistent with a previous study that demonstrated intact executive function in a PD-ICD group (Siri et al., 2010) and we did not see greater errors in the PD-ICD group compared to controls.

Pathological gamblers made fewer correct anticipations and made more errors compared with controls. Furthermore, their reactive saccades were non-significantly *slower* than those of controls. These effects contribute to an overall lower mean reward. In this way the PG group resembled the PD patients, but they out-performed them overall, perhaps because they were younger. This finding echoes that of a probabilistic decision-making experiment: All PD patients were impaired compared to the control group but the PD-ICD patients showed similar

addictive behaviours to illicit substance abusers, whereas PD patients *without* ICDs more closely resembled reward sensitive (and insufficiently punishment-averse) pathological gamblers (Furl and Averbeck, 2011).

*Lateral Reward task*

PD-ICD patients showed some (non-significant) speeding to rewarded targets similar to the control group. Gamblers, however, showed significant reward sensitivity manifest as saccadic speeding. The absence of such speeding in age-matched controls might suggest heightened reward sensitivity in the PG group. Results from neuroimaging studies in pathological gamblers show diminished ventral striatum and vmPFC/VLPFC activation during non-specific rewarding and punishing events in pathological gamblers compared to normal controls (Reuter et al., 2005; de Ruiter et al., 2008) implicating a blunted neurophysiological response to rewards as well as to losses in pathological gamblers. This is in contrast to our finding and suggests that what we are measuring is reward *drive* rather than sensitivity (Loxton et al., 2008).

*Reverse Traffic Light Task*

The reverse traffic light task was difficult for patients – particularly those who were impulsive - to complete. Pathological gamblers and the PD-ICD group performed similarly to age matched controls. We did not demonstrate greater risk taking (diminished risk aversion). We might have expected the PG group to demonstrate reduced risk aversion and hence produce a shorter Stop Anticipation Interval (SAI), as previous studies have suggested that diminished responsiveness is associated with the condition (van Holst et al., 2010; Loxton et al., 2008).

### 7.4.2 PD patients demonstrate reward insensitivity, low anticipation and slow responses whereas PD-ICD patients did not.

PD patients were slow in the SRT task compared to healthy controls. This may have been due to their greater age. Gamblers, PD-ICD patients and age-matched controls all demonstrated similar SRTs. We therefore replicated the finding that PD-ICD patients were faster than non-ICD PD patients in a previous study (Voon et al., 2009) but, unlike other authors (Siri et al., 2010), we have not failed to acknowledge the significance of age in generating this difference (see also Chapters 1 & 2). PD patients also showed lack of reward sensitivity in the lateral reward task. There were no age-matched controls for this task so the absence of reward sensitivity may be due to age and/or disease. Furthermore, the effects of drugs (including type, dose and duration of treatment) and the time of testing in relation to the time of medication administration could not be adequately controlled for in a study of this size.

Levodopa has been shown to improve reward sensitivity, but also to increase errors in the face of negative feedback (Czernecki et al., 2002; Kobayakawa et al., 2010; Rowe et al., 2008). Dopaminergic medications may also improve tasks requiring timing (Kw et al., 1994; Malapani et al., 1998; Pastor et al., 1992). The PD-ICD patients were, on average, taking more dopaminergic medication in total (and larger levodopa equivalent doses of dopamine agonists) than the PD group. These dose differences were not significant but higher dopamine doses may have contributed to some normalisation of performance due to both improvement in timing and heightened reward sensitivity.

### 7.4.3 There are some similarities but also significant differences between the pathophysiology of *de novo* pathological gambling and ICDs in PD

Both the PD-ICD and PG groups showed reduced anticipation in the Traffic Light Task but only the PG group committed more errors. Similarly, Go/Nogo performance is found to be impaired in gamblers, with both more errors and increased performance variability compared with controls (Kertzman et al., 2008). There are therefore similarities in the cognitive/executive deficits shown by pathological gamblers with those of PD patients, especially those with ICDs, however there are also important differences that may be evident in oculomotor task performance. Though this study failed to demonstrate significant group effects, there are trends toward differences in task performance that warrant further discussion and investigation.

There is experimental evidence for differences in the cognitive disturbances that cause *de novo* pathological gambling compared with those seen in PD-ICD patients. Frontal deficits are particularly implicated in the development of PG. There is a similarity between the behaviours of problem gamblers and patients with VMPFC lesions when attempting the IGT (Cavedini et al., 2002) and poor performance by gamblers in the Game of Dice Task, a risky decision-making task which is sensitive to dorsolateral PFC (DLPFC) damage (Brand et al., 2005). This has led to the suggestion that dysfunction in these (frontal) areas might also have a role in the pathophysiology of problem gambling. Low fMRI BOLD activation of the DLPFC is associated with impulsive scores on the BIS-11 (Asahi et al., 2004) a region known to be involved in oculomotor control (Kim and Shadlen, 1999; Pierrot-Deseilligny et al., 2005; Pierrot-Deseilligny et al., 2003). This may explain some of the (non-significant) differences between the PG group and controls.

### 7.4.4 Similarities and differences are task dependent

Whether or not the gambling tendency in PD-ICD is the same as that seen in otherwise healthy people may depend upon how the question is phrased – that is to say which measures are employed to answer it. In order to compare the neuropsychological impairments found in PD-ICD patients, substance abusers and pathological gamblers, a study using the bead task (a measure of subjects ability to make rational decisions about probability (Furl and Averbeck, 2011)). This investigation found that *all* PD patients made more impulsive and irrational choices than the control group. PD-ICD patients showed similar behaviour to illicit substance abusers, whereas patients *without* ICDs more closely resembled pathological gamblers. We did not replicate this finding, but our PD group was older than both the PD-ICD and PG groups.

In contrast, a functional imaging study has shown similarities between (disordered) brain activation in PG and that of alcohol dependent subjects. Both had significantly reduced activity in the ventromedial prefrontal cortex (VMPFC), insula, and ventral striatum during prospect and anticipation phases of both gains and losses. Furthermore, activity in the ventral striatum correlated inversely with levels of impulsivity in PG participants (Balodis et al., 2012). Impulse control disorders in PD, by contrast, are attributed to *excessive* dopaminergic stimulation of

ventral striatal projections to frontal areas such as orbitofrontal cortex (OFC) (Frank and Claus, 2006). OFC neurons are known to encode information about economic value (Padoa-Schioppa and Assad, 2006). *Lesions* of the OFC cause impairment in decisions related to the expected outcome of actions (Tremblay and Schultz, 1999). Dopaminergic striatal neurons activated in relation to the expectation and detection of reward show activity related to the preparation, initiation and execution of movements which reflect the expected reward (Schultz et al., 2000). ICDs in PD may therefore result from disordered dopaminergic striatal input to frontal areas.

### 7.4.5 Limitations of this study

Drug effects were not demonstrated in this experiment. To do so would require that either patients omit their medications for pre- and post- dose testing, which leads to travel difficulties, or the study of a far larger group such that the patient groups could be sub-divided according to treatment type/dose. Even then, there would still be a risk of confounding by disease severity (more severely affected patients are likely to be taking more medication). Neither is testing subjects "off" and then "on" without issue: Cognitive and behavioural effects of chronic medication may outlast many plasma half-lives of the drug, as a result of receptor changes in the brain (DiCaudo et al., 2012; Riverol et al., 2014). "Wash-out" periods of weeks or months are reported and employed in clinical trials (Fahn, 2006). The most effective method for cognitive assessment of drug effects in PD might be testing treatment naïve patients both before and after taking medication. This is both difficult to achieve and also tells us little about patients with more advanced disease.

Age effects are difficult to control for. Recruitment of healthy age matched controls in middle and older age groups is fraught with selection bias. Our older controls were noticeably different in personality (though not BIS-11 scores) from the middle-aged group. They were more likely to be retired and pursuing further education opportunities in the local area. They were generally volunteering as subjects for altruistic reasons and were less motivated by payment. Middle-aged male controls, however, were more likely to be unwillingly unemployed and motivated to participate by the payment. This may have led to inadvertent differences in personality-type that may have obscured other group differences.

### 7.4.6 Summary

There is evidence that dysfunction in multiple frontal and (especially ventral) striatal brain areas impacts upon both 1) rewarded decision-making and 2) oculomotor control. Furthermore, there are functional anatomic distinctions between pathological gambling as an impulse control disorder *in PD* and pathological gambling in otherwise healthy people. The Traffic Light Task and the rest of our battery of oculomotor tasks have revealed interesting findings in both PD, PD with associated ICDs and pathological gamblers. These findings warrant further investigation with larger subject groups, on and off medications and/or in combination with dynamic measures of focal brain function, such as fMRI or MEG.

# 8. Discussion

## 8.1 Summary of findings

The aim of the experiments described in this thesis was to establish the utility of rewarded oculomotor decision-making tasks as an index of motivated behaviour in age, disease and under the influence of drugs affecting dopaminergic neurotransmission. Here, I summarise the results of the six experimental chapters before discussing the implications of the findings, limitations of the studies and future investigations suggested by them.

### 8.1.1 The Traffic Light Task and the effects of Age

I developed a simple saccadic task, the Traffic Light Task (Figure 2.1), which measures decision-making when participants are required to make rapid choices (stay or go) under risk (Chapter 2). The task generated two groups of responses in young, healthy volunteers: a reactive distribution and an anticipatory distribution (Figure 2.3B). Separately parameterised linear rise-to-decision threshold processes model the two distributions well (Figures 2.6 & 2.8). Task performance, measured as reward obtained, correlated strongly with the percentage of anticipatory, correct responses (i.e., those which fall in the range 0-200ms after the GO signal). Participants had to take a decision about whether to stay and wait longer, or make a response before the green light, risking the possibility of a small penalty against a potentially large reward. Young adults made what might be called functionally useful anticipations (Dickman, 1990). They were willing to take a risk and make early responses because overall this would optimize overall reward. By contrast, older subjects demonstrated little evidence of anticipatory behaviour (Figure 2.10). Instead, the vast majority of their responses were triggered after the GO signal and, for them, reward simply correlated inversely with reaction time.

This finding of altered responding with age is recognised in a number of different reaction time and rewarded tasks e.g. (Chowdhury et al., 2013; Shohamy and Wimmer, 2013; Wolkorte et al., 2014), To our knowledge, age related changes in oculomotor decision-making have not previously been reported, however. Reductions in dopaminergic frontostriatal connections (especially between the ventral striatum and the prefrontal cortex (Kaasinen and Rinne, 2002; Erixon-Lindroth et al., 2005; Mell et al., 2009; Klostermann et al., 2012)) are a recognised correlate of the effects of healthy aging upon cognitive task performance. Such changes could reasonably be implicated in poor rewarded oculomotor task performance. Foraging tasks suggest a reduction in exploration with aging (Mata et al., 2013). The traffic light task requires exploration in early trials in order to establish the mean duration of the amber light. Older subjects are perhaps so punishment avoidant that they do not allow sufficient exploratory trials in order to establish an optimal strategy.

### 8.1.2 The relationship of traffic light task performance to other measures of oculomotor responding and motivated behaviours

In order to assess the various factors influencing traffic light task performance and to compare oculomotor task outcomes with self-reported impulsivity, I compared traffic light task outcomes with a number of other m**easures (Chapter 3).**

Mean **SRT Task** (Figure 2.2) saccade latency correlated significantly with mean reaction time in the Traffic Light Task, *negatively* with the ratio of Anticipations to Errors (AER) in the Traffic Light Task, and positively with latencies in the Lateral Reward task (both rewarded and unrewarded). Faster subjects were therefore likely to make more *correct early* responses than were slower subjects. SRT task performance was *not* correlated with personality scores or sub-scores (BIS-11 or TPQ), suggesting that *rewarded* tasks better index motivated behaviour.

The **lateral reward task** (Figure 3.2) demonstrated baseline non-significant reward-related speeding of saccade initiation in both young and middle aged volunteers. There was a negative correlation between rewarded and unrewarded mean saccade latencies and AER in the traffic light task. Negative correlations were also found between mean latencies and two BIS-11 sub-scores (the Motor factor and Attentional Impulsiveness dimension) – correlations that did not exist for the SRT task. A negative correlation between right dorsolateral prefrontal activity (BOLD response) during response inhibition in a Go/Nogo task also demonstrated correlation with Motor Impulsiveness on the BIS-11 (Asahi et al., 2004). Despite a lack of statistically significant reward-related speeding, it would appear that the Lateral Reward task is sensitive to something more than simple saccadic reaction time, and may be sensitive to reward-related (functional) impulsivity which is dependent upon functional ventrostriatal-prefrontal connections.

The **reverse traffic light (RTL) task** (Figure 3.4) allows insight into subjects' willingness to take risk. It is independent of motor reaction times as the decision to initiate the saccade is made without the trigger of any novel stimulus. A positive correlation between mean reward in this task and the Anticipation:Error Ratio (AER) in The Traffic Light Task suggests that similar traits are required for task success – qualities such as sensitivity to reward and willingness to take risk, may be required to perform optimally in both tasks. Reward in this task is significantly correlated with the Attentional Impulsiveness (AI, second order factor) score of the BIS-11. The inverse relationship between mean SRT and AER in concert with a positive correlation between AER and mean RTL rewards fits with a model of successful traffic light task performance that depends upon a combination of speed, timing, reward sensitivity and willingness to take risk. Oculomotor performance correlations between tasks and with BIS-11 factors support the inference that the tasks might be sensitive to impulsivity as defined by other recognised and validated measures. Attentional impulsiveness has been shown to correlate with increased errors in measures of response inhibition and poorer choices in the Iowa Gambling Task (Christodoulou et al., 2006). Iowa Gambling task performance is sensitive to prefrontal cortical function (Bechara et al., 2005; Brevers et al., 2013; Lawrence et al., 2009). Similar correlation with reward here lends support to a hypothesised role for this region in reverse traffic light task performance.

### 8.1.3 Dopaminergic modulation of oculomotor responses in a patient with apathy due to bilateral pallidal lesions

I used these novel probes of oculomotor decision-making to demonstrate relative insensitivity to reward in an individual with apathy following bilateral GPi lesions (Chapter 4). KD initially made very few anticipatory responses in the traffic light task compared with age-matched controls (Figure 4.6A). Pallidal outflow to posterior medial frontal cortex (Alexander et al., 1986) is implicated in modulating cortical error-related activity (Herrojo Ruiz et al., 2014). Absence of this information may lead to avoidance of risky strategies such as anticipatory responding (similar to that seen in Parkinson's disease (Crawford et al., 1989).

Dopaminergic therapy, first with levodopa and then with ropinirole, increased anticipatory responses to within the normal range (Figure 4.6B). The lateral reward task demonstrated that KD had SRTs within the normal range but showed no speeding to the rewarded side (RS), unlike healthy volunteers (Figure 4.7). Treatment with levodopa led to reward sensitivity, with speeding of responses to the RS and slowing to the unrewarded side compared to baseline. Off medication, the difference in SRTs to rewarded and unrewarded targets became non-significant. Subsequently on ropinirole, a direct dopamine $D_2/D_3$ receptor agonist, KD again demonstrated reward sensitivity, as well as generalized speeding. These effects on dopaminergic medication were associated with clinical improvement, reduction of apathy and increased motivation to find work and in social interactions – most prominently while on the dopamine agonist. The findings demonstrate a causal relationship between basal ganglia function and motivation or willingness to make an effort for reward. They provide proof-of-concept data for the treatment of apathy which is increasingly recognized to be a key component of several neurological disorders (Marin, 1991; Bonelli and Cummings, 2008; Chow et al., 2009; Starkstein et al., 2009).

### 8.1.4 Dopaminergic modulation of oculomotor responding in healthy volunteers

In order to qualify these dopaminergic effects further, we used both **levodopa** (Chapter 5) and **methylphenidate** (Chapter 6) to investigate their impact upon oculomotor decision-making in healthy controls. As hypothesised, the effects of training across sessions were prominent in both experiments (Figures 5.1, 5.5, 5.6, 5.10, 6.4, 6.5, 6.7, 6.8) a factor often ignored in drug/placebo experiments.

Analysis of variance demonstrated a non-significant interaction between the L-dopa/placebo condition and the session in the **SRT task** (Figure 5.2), suggesting that the order of drug/placebo administration might be important. The apparent drug effect was of slowing responses compared to placebo in the second session, whereas it had no significant effect in the third session. This may be a true difference due to dopaminergic modulation having effects on relatively novel tasks as compared to previously trained ones. Latencies were non-significantly reduced by MPH compared to placebo (Table 6.1), consistent with previous studies which have shown shorter reaction times under the influence of this drug (Klein et al., 2002; Mostofsky et al., 2001). Greater subject numbers might render this a statistically significant effect.

Analysis of variance in the **Traffic Light Task** demonstrated a non-significant interaction between L-dopa/placebo condition and session with respect to error rates (Figure 5.7). In the second session, L-dopa appeared to reduce error rates compared to placebo, in the 'drug first group'. Conversely, in the third session, when the 'placebo first' group were given L-dopa, more errors were made than by the placebo group. There was a trend toward *fewer* early responses with methylphenidate (both correct, highly rewarded anticipations and punished errors, Figure 6.4). If truly representative, this trend might reflect a reduction in impulsivity due to methylphenidate (DeVito et al., 2008b) or reflect improvements in timing (Rubia et al., 2009). Learning effects across epochs of 100 trials were similar in the drug/placebo condition, and performance had already reached a plateau after the training session.

In the **reverse traffic light task**, designed to assess risk seeking and relatively independent from reaction time, the main effect was of training, with subjects becoming increasingly willing to risk an error in order to reap greater rewards on successful trials (Figures 5.10 & 6.7). With each session, the distribution of saccades shifted rightward (Figures 5.11 & 6.8). There was a significant reduction in the mean STOP anticipation (the degree to which subjects accurately anticipated the red light) between sessions 1&2 ($p<0.01$) and a strong trend toward a further reduction in Session 3 ($p=0.05$). The task is designed to measure willingness to take risks, as it requires responses to be made *as late as possible* in order to accrue the greatest reward. There was no evidence of a change in risk seeking/avoidance resultant from either L-dopa or MPH.

In the **lateral reward task**, there was a non-significant interaction for latencies to rewarded targets between the L-dopa/placebo condition and session (Figure 5.12). It would appear from these results that receiving L-dopa in the first session, enhanced the learning effect, leading to even faster responses to rewarded targets in the second session. One could interpret that the 'drug first' group were slowed by L-dopa in the first session but were able to exploit enhanced learning in the second session, when they were faster and drug free. The 'placebo first' group, by contrast, had no enhanced learning and were slowed down by L-dopa in the second session, leading to an apparent diminished learning effect. This may, however, represent a chance "ceiling effect" due to the 'placebo first' group being faster overall just by chance. There was a consistent finding of reward-sensitive speeding overall in the lateral reward task. There was significant improvement following training but no difference between unrewarded and rewarded saccade latencies due to methylphenidate.

### 8.1.5 Parkinson's Patients and Impulse Control Disorders

Pathological gamblers were significantly more impulsive according to **BIS-11** scores, as found in previous studies (Martins et al., 2004) but there were no significant differences between PD patients (with or without ICDs) compared with age-matched controls. PD patients were slow in the SRT task compared to healthy controls (Figure 7.6). Responses in the SRT task were also slow and highly variable. This may have been due to their greater age. Gamblers, PD-ICD patients and age-matched controls all demonstrated similar SRTs. We therefore replicated the finding that PD-ICD patients were faster than non-ICD PD patients in a previous study (Voon et al., 2009) but, unlike other authors (Siri et al., 2010), we have not failed to recognise the significance of age in generating this difference (see also Chapters 1 & 2).

In the **Traffic Light Task**, PD patients made significantly less reward than healthy, age-matched controls due to a combination of a more errors, fewer correct anticipations and slower reactive saccades (Figure 7.3). Anticipatory responses in the Traffic Light Task were non-significantly greater in *number* than controls. This suggests that PD patients continued to make early responses despite higher error rates, and therefore failed to learn from negative feedback. This is a feature of other studies of reward learning in PD where intact learning from positive feedback is seen but there is a lack of response to negative feedback, or aversive learning (Cools, 2006; Rowe et al., 2008).

PD-ICD patients demonstrated a trend toward fewer rather than more anticipatory responses in the Traffic light Task compared with controls (Figure 7.4), in contrast to the PD group. This may suggest greater fronto-striatal dysfunction in the PD group compared to PD-ICD (Santangelo et al., 2009), however, the PD-ICD group were also younger, so it is not possible to separate the contributions of age and impulsivity in this study. This result is consistent with a previous study that demonstrated intact executive function in a PD-ICD group (Siri et al., 2010).

Pathological gamblers made fewer correct anticipations and made more errors compared with controls (Figure 7.7). Furthermore, their reactive saccades were non-significantly *slower* than those of controls (Figure 7.8). These effects contribute to an overall lower mean reward (Figure 7.9). In this way the PG group resembled the PD patients, but they out-performed them overall, perhaps because they were younger.

In the **Lateral Reward Task**, PD-ICD patients showed (non-significant) speeding to rewarded targets similar to the control group. Gamblers, however, showed significant reward sensitivity manifest as saccadic speeding. The absence of such speeding in age-matched controls might suggest heightened reward sensitivity in the PG group. PD patients showed lack of reward sensitivity in the lateral reward task. There were no age-matched controls for this task so the absence of reward sensitivity may be due to age and/or disease. The reverse traffic light task was difficult for patients – particularly those who were impulsive - to complete. Pathological gamblers and the PD-ICD group performed similarly to age matched controls.

## 8.2 General Discussion

### 8.2.1 Conclusions

We have demonstrated that these novel oculomotor tasks are sensitive to reward motivated behaviour in a clinically relevant manner. We have also demonstrated the significance of the effects of age and training – often ignored in other reported behavioural studies. We did not demonstrated main effects of either levodopa or methylphenidate on rewarded decisions in healthy volunteers. This and the lack of main effects (or obscuration by age effects) between the groups described in Chapter 7 may reflect the number of subjects studied.

### 8.2.2 The current knowledge of oculomotor impulsivity

Oculomotor impulsivity has tended to be defined as a deficiency in inhibitory control. Accordingly it has been interrogated through the use of pre-potent response inhibition (e.g. stop signal, Go/Nogo, antisaccade and countermanding tasks) (Roberts et al., 2011). Others have proposed alternatives such as a visual pursuit task (Cirilli et al., 2011) in which an anticipatory saccade is provoked by the delayed appearance of a pursuit target. This is similar to express saccades (Fischer and Ramsperger, 1984) other than that the expected response is a pursuit movement as opposed to a single saccade. The measurement (and modulation) of bimodal reaction time distributions as an index of behavioural motivation described here is a novel one.

### 8.2.3 The Significance of early (saccadic) response distributions

The cognitive significance of these early saccadic response distributions remains somewhat unclear. If we assume that early responses form a completely separate group of saccades from the more typical, "reactive" saccades (albeit one that might overlap in latency), then we might suggest that such saccades arise from a discrete "short circuit" which bypasses procrastinating "modules". This circuitry might be less susceptible to inhibition by cortical regions or other basal ganglia nuclei. Support for such a hypothesis arises from computational models derived from rewarded saccadic tasks (N'guyen et al., 2014). This model proposes that, after a period of learning, saccades can be triggered by a "hyper-direct" pathway from retina to superior colliculus,. This pathway is normally inhibited ("braked") by the basal ganglia, preventing it from initiating saccades. We might hypothesise that impulsivity is due to inappropriate release (or the absence) of this brake – for example due to the actions of dopamine agonists in PD-ICD, changes in fronto-striatal circuitry in ADHD or a focal brain lesion. Conversely, apathy may be due to either excessive inhibition/braking or the inability to learn and thereby release the brake. The low rate of anticipatory responding in older age and in PD potentially supports a dopaminergic role in "unbraking" – since both conditions are associated with dopaminergic deficits in frontal and/or striatal circuitry. This effect may not be specific to saccades. We (and others e.g. (Machado-Pinheiro et al., 1998)) have demonstrated early response distributions in manual tasks. A manual version of the traffic light task (using a button box response) produces a similar bimodal response distribution, supporting the existence of a modality independent mechanism for early responses (Heyes et al., 2012).

### 8.2.4 What does the Traffic Light Task Measure?

One explanation for the findings is that the Traffic Light task is sensitive to deficits in "functional" impulsivity – whether impaired by age, PD or focal lesions of the basal ganglia (Figure 8.1) – but less so to "dysfunctional" impulsivity (as may be elevated by drugs or impulse control disorders). Furthermore, although trait impulsivity is frequently correlated with neurocognitive mechanisms involved in response monitoring and inhibition, the same is not necessarily true of mechanisms of self-regulation and decision making (Perales et al., 2009). We did find more errors in both pathological gamblers and patients with Parkinson's disease but the effects did not reach statistical significance. It is possible that more extreme disinhibition, as found in frontal lobe lesions and/or attention deficit disorder, might manifest in a more left-shifted anticipatory distribution (Figure 8.1), demonstrative of persistent early responding in the face of errors. Attempts to study patients with these pathologies were stifled by profound difficulties in attending to the oculomotor tasks and/or their ability and/or willingness to attend for testing sessions. Nevertheless, it would be instructive to attempt to improve the anticipation of PD patients and/or older volunteers by administration of dopaminergic drugs. Modulation (of reward prediction error) in older healthy volunteers has been demonstrated using levodopa but this required a larger cohort (n=32) *and* post hoc division of the group into low and high performers to achieve a statistically significant result (Chowdhury et al., 2013).

### 8.2.5 Confounds of time estimation and speed/accuracy trade- off

A potential criticism of the Traffic Light Task (in forward and reverse guises) is its dependence upon subjects' ability to estimate, remember and reproduce time intervals. Deficits in time interval estimation are found in both healthy aging and in neurodegenerative basal ganglia disorders (Gunstad et al., 2006; Parker et al., 2013; Rubia et al., 2009; Wild-Wall et al., 2008). However, these studies focus upon longer durations in the seconds to minutes range. Shorter intervals, in the millisecond range, are consistently spared in patients with PD (Cope et al., 2014; Smith et al., 2007b). Work subsequent to that described in this thesis used a time estimation task in tandem with the Traffic Light Task and found that ability in the time estimation task did not explain variability in Traffic Light task Performance (Burnett Heyes et al., 2012). One might assume that impulsive subjects would tend to respond too quickly and thereby incur more errors (thereby producing a left shift in the anticipatory distribution of traffic light task responses). However, evidence suggests that this may be an oversimplified view (e.g. (Dickman and Meyer, 1988)**)**. In a reaching task, where a motor response direction was cued at different levels of uncertainty, there was an interaction between BIS-11 impulsivity score, gender and level of uncertainty in the task but no main effect of impulsivity on precision errors or RT (Tzagarakis et al., 2013). Further analysis of the effect of RT and impulsivity on precision errors showed a different pattern for high versus low impulsives in the high uncertainty condition. In addition, there was a significant early error speed-accuracy trade-off for women, primarily under low uncertainty but a 'reverse' speed-accuracy trade-off for men in the high uncertainty condition. These results further define impulsivity as a behavioural trait that modulates speed versus accuracy response styles depending on environmental constraints.

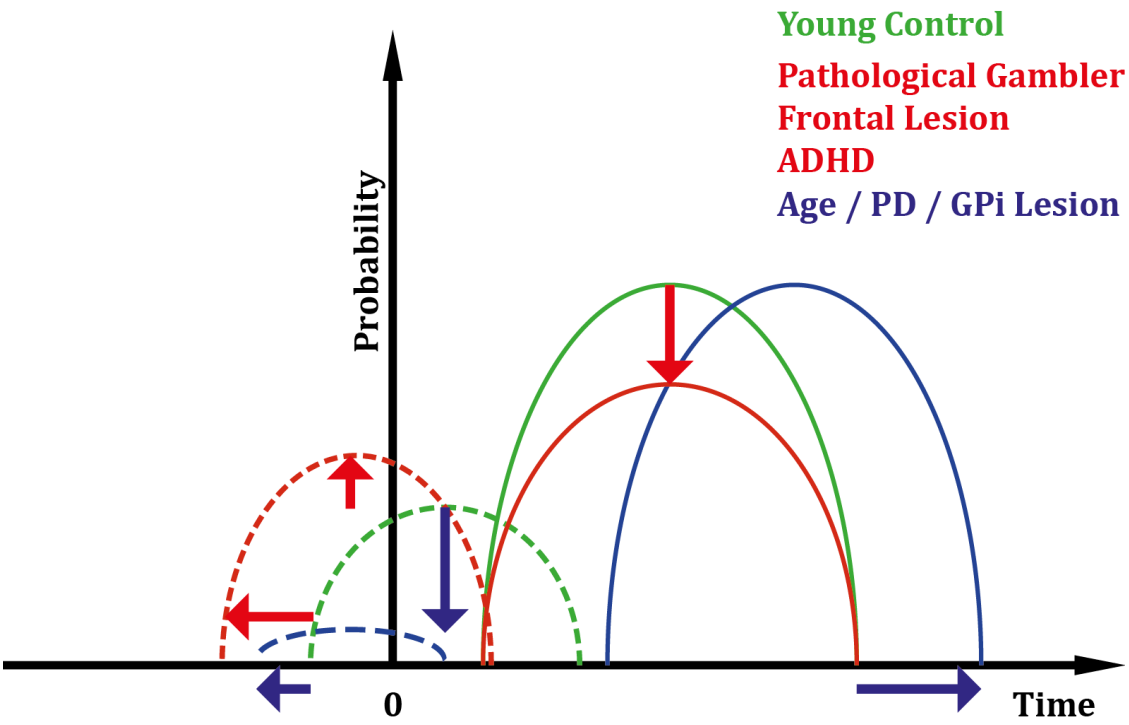



**Figure 8.1 Hypothesised Traffic Light Task Saccadic Probability Distribution Effects**

Age and/or Parkinson's Disease and focal basal ganglia (GPi) lesions caused a large reduction in (or the absence of) anticipatory responding and an increase in errors (Chapters 2,4 & 7). This was reversed by levodopa and ropinirole (a dopamine agonist) in the patient with GPi lesions (Chapter 4). We might hypothesise that dopaminergic drugs could have a similar effect on older volunteers and those with PD. Furthermore, dopamine might also lead to speeding of reactive saccades, thereby normalising both distributions.

In contrast, patients with frontal lesions or ADHD and pathological gamblers might demonstrate increased anticipatory responding but with a leftward shift in the distribution – leading to more errors and poorer overall performance. Such deficiencies might respond to methylphenidate. In contrast, due to their already "optimal" dopamine levels, young controls would not benefit from either drug.

It is unclear whether the dopamine agonist effects in Parkinson's Patients with Impulse Control Disorders (PD-ICD) would lead to patterns consistent with the proposed pathological gambler/frontal lesion hypothesis or simply improve their responding such that it matched that of healthy controls. A larger study is needed to investigate this. Furthermore, we might seek to investigate patients with more extreme disorders of disinhibition (such as in frontal lesions and ADHD) and attempt to improve their performance using methylphenidate.

### 8.2.7 Mesolimbic dopamine and reward

Experimental evidence for dopaminergic roles in decision-making supports a hypothesis of functional and neurochemical reciprocity between the striatum and the prefrontal cortex (Figure 8.2A, (Cools, 2008)). This suggests that optimal DA levels in the striatum are required for cognitive flexibility (a lack thereof leading to inflexibility), whereas optimal levels allow for cognitive stability in the PFC, where a lack causes *distractibility*. If distractibility leads to impulsive behaviours, we might anticipate impulsive oculomotor responding in frontally depleted states such as those demonstrated in aging (Bäckman et al., 2006) and pathological gambling (Reuter et al., 2005). However, coincident lack of cognitive flexibility due to concurrent striatal DA depletion may reduce exploratory behaviour and anticipatory responding in tasks like the traffic light task. Dissociating the effects of Parkinson's Disease and age has proven difficult using oculomotor tasks, but imaging studies suggest that there are differences in both anterior cingulate responses to reward feedback and diminished connectivity between midbrain and ventral striatum (Schott et al., 2007).

A limitation in the patient studies was sample size – both in numbers of individuals and in numbers of responses. Neurophysiological recordings in macaques benefit from many more (thousands of) data points, albeit in a few (often only 2) highly trained individuals. Recording fewer trials in humans requires the comparison of group means. There is greater vulnerability to noise as a result of inter-individual variability. It is also difficult to control for sustained attention during a 1 hour long testing session - humans may be less motivated by the increasing "money bank" displayed on the screen compared to macaques receiving immediate juice or food rewards.

### 8.2.8 How might we otherwise demonstrate drug effects?

Though we did not demonstrate main effects of either levodopa or methylphenidate in young healthy volunteers, this may be due to (a failure to disrupt) their already optimal baseline dopamine levels for the task. We might not have chosen the optimum dose to demonstrate the greatest effect. This is not necessarily the highest dose, as demonstrated by other experiments with levodopa and MPH (Linssen et al., 2014b). It is also possible that a genetically heterogeneous group might demonstrate opposing effects of the drug, thus negating potential differences (through regression to the mean). Furthermore, there may also be dopaminergically derived individual differences in the amount of effort people are willing to expend for reward (Treadway et al., 2012). Risk taking is associated with DAT1 polymorphisms when subjects perform the Balloon Analogue Risk Taking Task (BART, see Chapter 3 (Mata et al., 2012)). Genetic variability affects the response to L-dopa (Eisenegger et al., 2010) and to stimulant drugs (Hart et al., 2012) including MPH in ADHD (Hong et al., 2012; Park et al., 2012; Roman et al., 2004). Segregating subjects by baseline performance and/or genetic polymorphisms (see (Passamonti et al., 2006; Boettiger et al., 2007; Eisenberg et al., 2007; White, 2008; Congdon et al., 2008; Levy, 2009; Paloyelis et al., 2010)) may enhance experimental results and lead to greater insights into the mechanisms of rewarded decisions.

### 8.2.8 Other neurotransmitters are implicated in impulsivity

That dopaminergic drugs are recognised as a risk factor for the induction of impulsivity in PD is due, in part, to treatment bias. Drugs that modulate other neurotransmitters are less frequently employed in PD and so the evidence for their contribution is not as strong. However, other studies – in animals and in humans - implicate neurotransmitters, such as noradrenaline (NA), gamma-amino-butyric acid (GABA) and serotonin (5HT) in impulsivity (Boy et al., 2011; Dalley and Roiser, 2012; Economidou et al., 2012; Robinson et al., 2008; Seo et al., 2008; Swann et al., 2013). Recent studies using response inhibition tasks demonstrate a benefit from both serotonergic and adrenergic drugs in patients with PD (Kehagia et al., 2014; Ye et al., 2014a, 2014b). It is possible that oculomotor effects in healthy volunteers are also more amenable to modulation by adrenergic or GABAergic (Hikosaka and Wurtz, 1985) drug effects. Serotonergic effects on decision making have been demonstrated through tryptophan depletion, which increased impulsive responses and increased attentional capacity (Fikke et al., 2013), this would be a potential method of modulation of traffic light task responding, but one for which the clinical relevance is less obvious.

### 8.2.9 The relevance of the ventral striatum to oculomotor responses

The ventral striatum is demonstrated to be instrumental in the determination of rewarded decision-making (Kable and Glimcher, 2007; Schultz et al., 1992) and is a neural correlate of abnormal cognition in aging (de Jong et al., 2012; Penner and Mizumori, 2012), PD (MacDonald et al., 2013, 2011), PD with ICDs (Evans et al., 2006) and PG (Koehler et al., 2013; Linnet et al., 2010). Furthermore, methylphenidate is demonstrated to exert its effects in ADHD by increasing dopamine at that location (Volkow et al., 2012) and L-dopa specifically impairs ventral putaminal activation for sequence learning in PD (Kwak et al., 2012). This and other evidence has led to the proposal of functionally distinct dorsal fronto-striatal circuitry for "higher order" cognitive processes and ventral limbic-striatal circuitry for motivational processes (Figure 8.2B). However, there is evidence to suggest that although both dorsal and ventral striatal circuitry is involved in the *anticipation* of potential future rewards, only the *dorsal* striatum and its connections to cortical networks are involved directly in the modulation of *oculomotor behaviour* by motivation (Harsay et al., 2011). This might explain sparing of rewarded oculomotor task effects from ventral striatal abnormalities, and mean that our tasks are more likely to reflect changes in the dorsal circuitry. The two regions do not act in isolation, however, and a model where the "flow of (dopaminergic) information" from ventral to dorsal striatum links "limbic" motivational (e.g. reward) salience to motor output via regions susceptible to "top down" cognitive control (especially from frontal cortical areas) is perhaps more convincing than a discrete "modular" approach (Figure 8.3, (Aarts et al., 2011)).

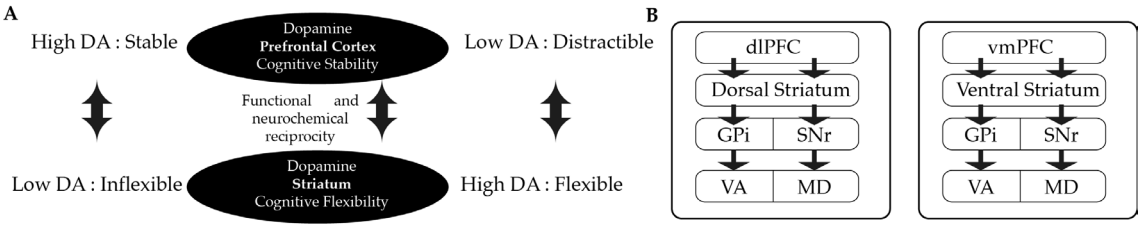



**Figure 8.2 Functionally Distinct Dorsal and Ventral frontostriatal circuits**

A Motivational processes are thought to involve ventral limbic-striatal circuitry whereas 'higher order' cognitive processes implicate dorsal fronto-striatal circuitry. PFC – prefrontal cortex, GPi – Globus Pallidus interna, SNpr – Substantia Nigra pars reticulata, VA – ventral anterior thalamus, MD – medial dorsal thalamus

B The working hypothesis stating that dopamine in the prefrontal cortex promotes cognitive stability, whereas dopamine in the striatum promotes cognitive flexibility. The functional opponency between stability and flexibility parallels neurochemical reciprocity between dopamine in the prefrontal cortex and dopamine in the striatum. DA = dopamine

*Adapted from (Cools, 2008)*

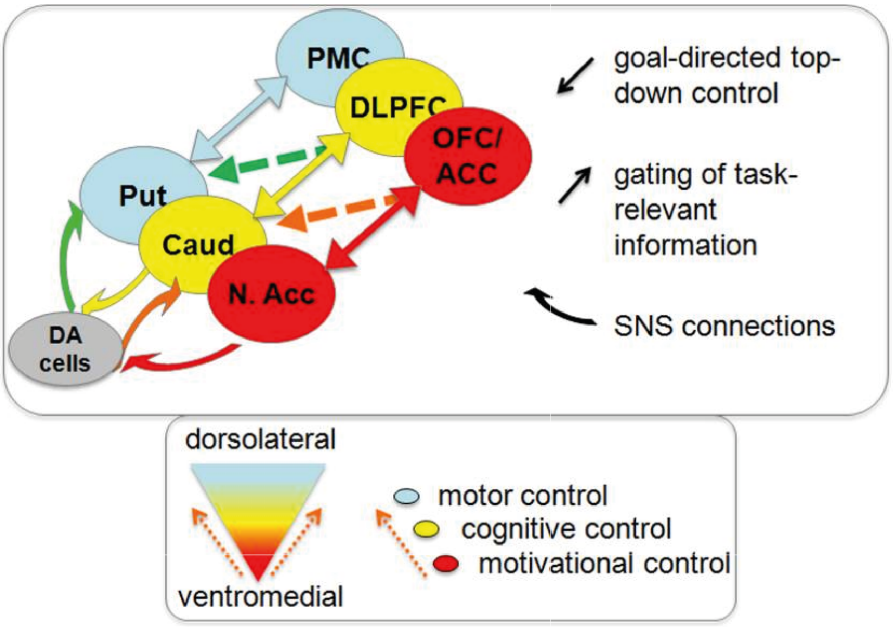



**Figure 8.3 Ventromedial to dorsolateral direction of information flow through frontostriatal-nigral circuitry.**

Interactions between the different frontostriatal loops involved in motivational control (red), cognitive control (yellow), and motor control (blue) can take place at the level of the striato-nigral-striatal (SNS) connections (bend arrows) or at the level of the fronto-striatal connections (straight arrows). The direction of information flow is always from ventromedial to dorsolateral regions in the frontostriatal circuitry. *SNS, striato-nigral-striatal; N. Acc, nucleus accumbens (ventromedial striatum); Caud, caudate nucleus (dorsomedial striatum); Put, putamen (dorsolateral striatum); OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; PMC, premotor cortex (Aarts et al., 2011).*

### 8.2.10 Combined imaging and electrophysiology enable the temporal and spatial precision required to elucidate the neural substrates of oculomotor decisions

To gather evidence for such models using oculomotor behaviour in humans, more complex methods may be required. Dynamic imaging studies in humans are limited in resolution but are increasingly able to measure subcortical changes in BOLD response. Combination with electrical measures enables event related information gathering at higher temporal resolutions. Studies of prepotent response inhibition (including antisaccades) have successfully combined both neurophysiological measures such as magneto encephalography (MEG e.g. (Boehler et al., 2009)), electroencephalography (EEG e.g. (Huster et al., 2013; Mueller et al., 2009)), or both e.g. (Astle et al., 2012) - often in combination with structural and/or functional neuroimaging e.g. (Smith et al., 2013; Lavallee et al., 2014). This allows reasonable temporo-spatial quantification of the substrates of behavioural tasks. Similar techniques could reasonably be applied to the oculomotor decision making tasks in this thesis in order to better understand the relative contributions of the various components of the cortico-striatal circuitry.

Through combinations of imaging (e.g. fMRI and PET) studies, consistencies emerge in the neural circuitry required for pro- and anti-saccades (for meta-analysis see (Jamadar et al., 2013)). Similar techniques might yield a neural correlate for braking mechanisms on a retino-tectal "escape" circuit (N'guyen et al., 2014) that otherwise leads to early saccades. Deficiencies in these braking areas might then be investigated as a locus for impulsive decision-making.

### 8.2.11 Toward models of rewarded oculomotor decision making

Since the early descriptions of cortico-basal ganglia-thalamo-cortical loops (Alexander et al., 1986), many hundreds of models of the circuitry have been developed in order to explain cognitive functions in various domains (Pennartz et al., 2009). Some of these attempt to combine elements of limbic and oculomotor loops and thereby explain rewarded oculomotor decision-making (Fee, 2012; N'guyen et al., 2014; Sato and Hikosaka, 2002; Soltani et al., 2013). The output of the BG can be thought of as having discrete motor "channels." In a simple model (that explains speeding to rewarded targets in the lateral reward task), these channels can be driven by sensory inputs from cortex. Neurons in the substantia nigra *pars reticulata* (SNr) are tonically active and inhibit the generation of saccades by the superior colliculus. SNr neurons can be inhibited by spiking in medium spiny neurons in the striatum, thus releasing the superior colliculus from inhibition (Hikosaka et al., 2000b). During training, rewarded saccades are generated with a shorter latency than saccades in the unrewarded direction. This behavioural change is thought to be mediated by activation of medium spiny neurons in the rewarded "channel" by the appropriate cortical inputs. The output of the SNr biases saccade generation by a projection to intermediate "motor" layers of SC. This model would likely be disrupted by the known changes in dopaminergic connectivity in GPi lesions (Chapter 4), Parkinson's Disease (Chapter 7) and Age (Chapter 2) (Figure 8.5).

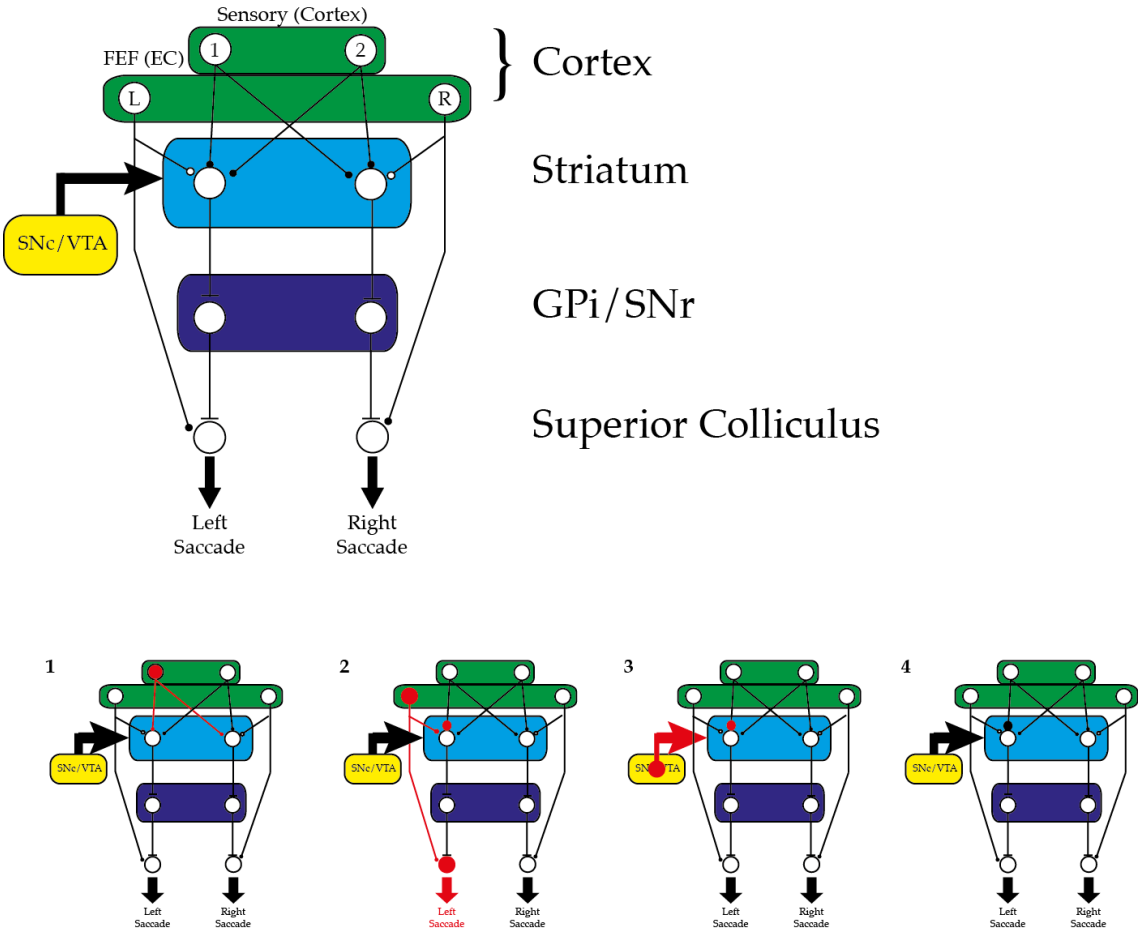



**Figure 8.4 Schematic diagram of a reward modulated oculomotor circuit in the basal ganglia (BG).**

The output of the BG can be thought of as having discrete motor "channels." In this simple model, these channels can be driven by sensory inputs from cortex. Neurons in the substantia nigra *pars reticulata* (SNr) are tonically active and inhibit the generation of saccades by the superior colliculus. SNr neurons can be inhibited by spiking in medium spiny neurons in the striatum, thus releasing the superior colliculus from inhibition (Hikosaka et al., 2000b). During training, rewarded saccades are generated with a shorter latency than saccades in the unrewarded direction. This behavioural change is thought to be mediated by activation of medium spiny neurons in the rewarded "channel" by the appropriate cortical inputs. The output of the SNr biases saccade generation by a projection to intermediate "motor" layers of SC.

*Adapted from (Fee, 2012)*

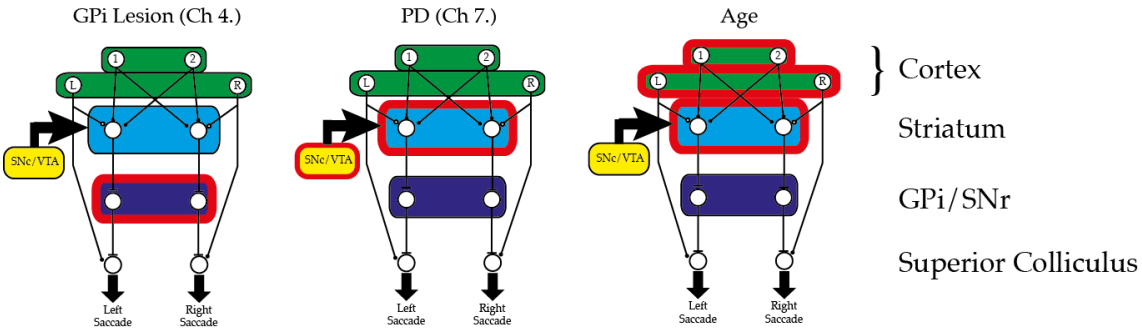



**Figure 8.5 Hypothesised sites of disruption of oculomotor reward learning**

This model of reward learning provides an explanation for the absence of reward sensitivity (as measured by the lateral reward task) in the patient with bilateral GPi lesions (Chapter 4), patients with PD (Chapter 7) and, hypothetically, in normal aging. Sites of abnormal function are outlined in red.

*Adapted from (Fee, 2012)*

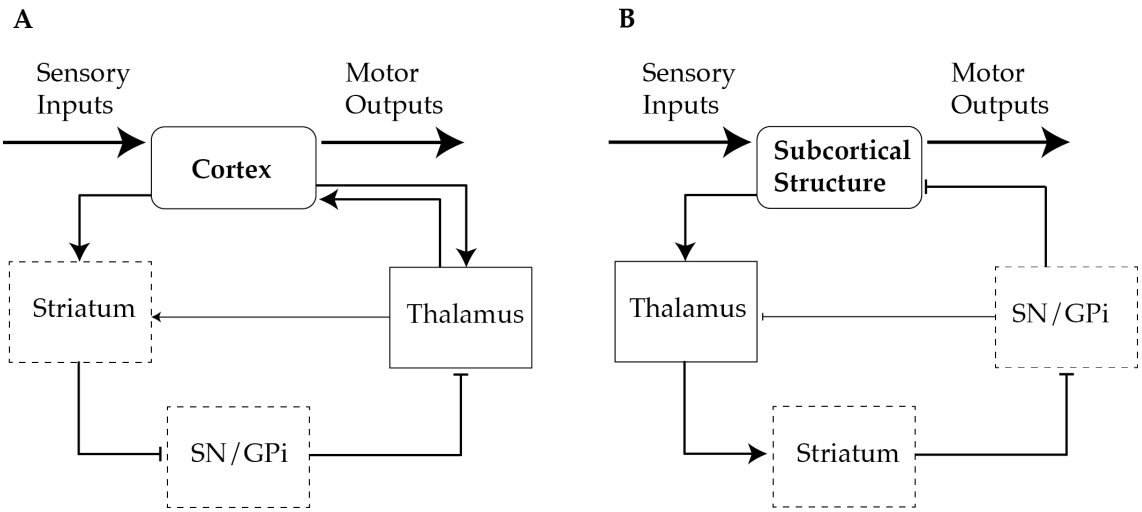



**Figure 8.6 Separate cortical and subcortical loops**

A General organisation for cortical loops

B General organisation for subcortical loops

Arrowheads indicate excitatory connections, perpendicular lines indicate inhibitory connections. Dashed lines indicate inhibitory centres. The thalamic nuclei involved differ between circuits: A (ventral anterior, ventrolateral, medial dorsal); B (pulvinar, lateral posterior, rostral and caudal intralaminar). *SN – Substantia Nigra; GPi – Globus Pallidus interna*

*Adapted from (McHaffie et al., 2005)*

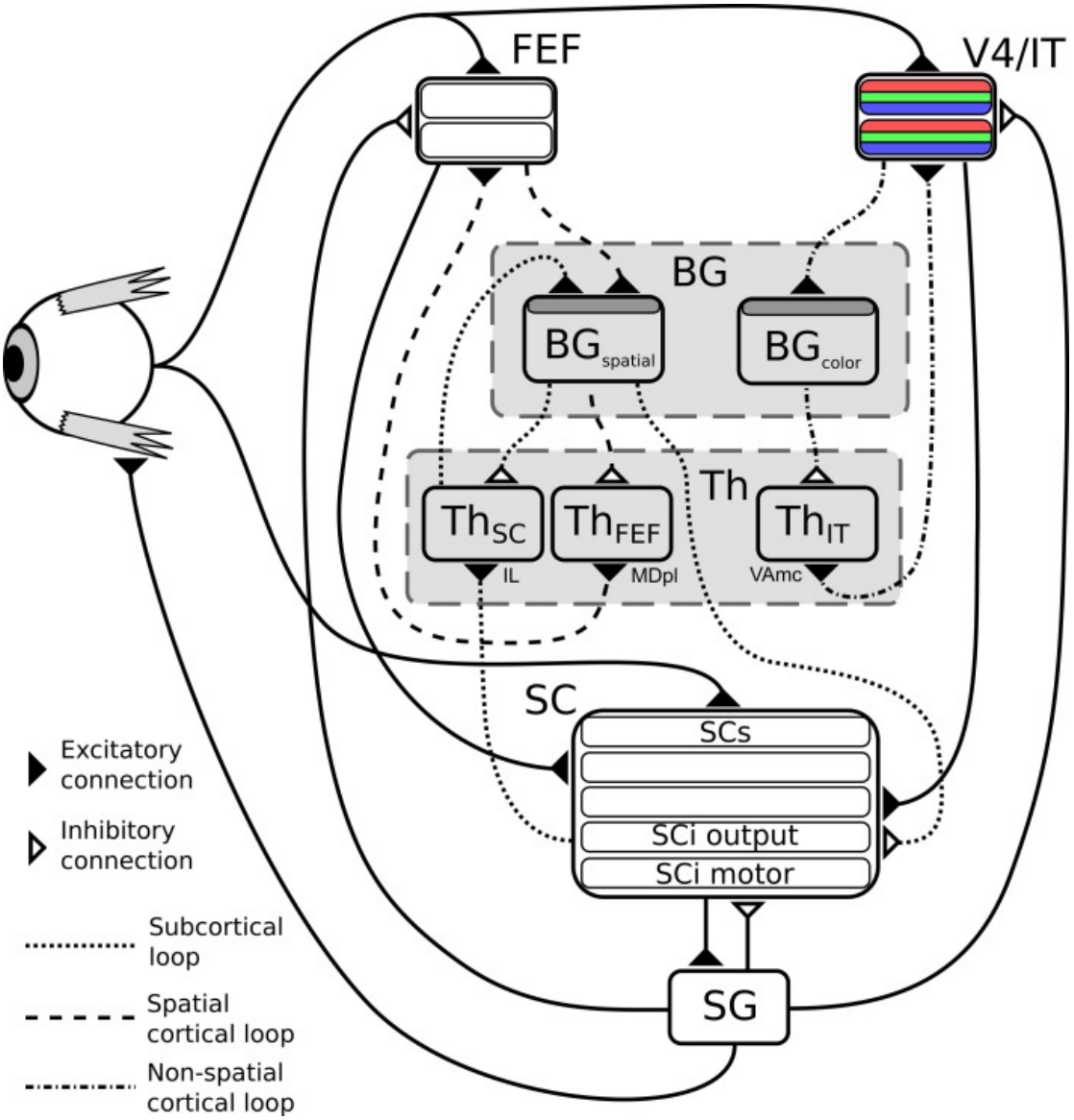



**Figure 8.7 Structure of a model which predicts early response distributions.**

Dark gray shaded layers on BG modules are input layers with reinforcement learning capabilities (N'guyen et al., 2014)

BG - Basal ganglia; FEF – frontal eye fields; SG – saccade generators; SC – superior colliculus; Th - thalamus; V4|IT, - Feature perception area including IT (TE region) interacting with V4 visual cortex area.

### 8.2.12 Subcortical "short cut" loops to explain early response distributions

Responses in the traffic light task are driven by more complex stimuli. Visual (exogenous) information such as red (trial start) and then amber light onsets interact with the subject's experience of previous trials, in terms of both amber durations and previous reward (endogenous information). This necessitates a more complex model. One such recently proposed model (Figure 8.8 (N'guyen et al., 2014)) invokes separate but similar subcortical (as opposed to cortical) basal ganglia loops (McHaffie et al., 2005) which learn concurrently to produce saccades (Figure 8.6). This model (Figure 8.7) produces short latency saccades after a period of learning, and, though it cannot account for early saccades produced spontaneously (as in express saccades (Fischer and Ramsperger, 1984), it may neatly explain the existence of early distributions in tasks like the traffic light task. Separate LATER units (Carpenter and Williams, 1995) might arise and drive saccades from each circuit and are modulated by reward learning which depends upon striatal D1 and D2 dopaminergic neurons. This is compatible with other recent (non-saccadic) models of reward learning in the basal ganglia e.g. (Clark and Dagher, 2014).

## 8.3 Summary

The experiments in this thesis describe novel and adapted oculomotor tasks which demonstrate oculomotor reward sensitivity and learning through both reduction in response latency and separate early distributions of anticipatory saccades. Impairments in these effects are dissociable but seem to occur together in both healthy aging and Parkinson's Disease. Increased erroneous responding in gamblers and PD patients with impulse control disorders was present but did not reach statistical significance. There were common correlations between the tasks described here with BIS-11 sub scores similar to those previously reported in association with both pre-potent response inhibition tasks and gambling tasks. This suggests that our tasks might also index abnormal fronto-striatal circuitry, particularly relating to the prefrontal cortex. Whether oculomotor tasks are somewhat protected from ventral striatal abnormalities remains uncertain.

Further research, using other drugs, or in combination with known genetic polymorphisms may enable further insights into the chemical effects upon oculomotor decision making in humans. Combination of neurophysiological techniques with dynamic imaging might enable a higher yield of spatial and temporal information (from manageable sample sizes) to inform future models of oculomotor decision making which otherwise rely heavily on animal work.

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# Appendix

## i The Barratt Impulsiveness Scale

DIRECTIONS: People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. Do not spend too much time on any statement. Answer quickly and honestly.

① Rarely/Never ② Occasionally ③ Often ④ Almost Always/Always

| | | | | | |
|---|---|---|---|---|---|
| 1 | I plan tasks carefully. | ① | ② | ③ | ④ |
| 2 | I do things without thinking. | ① | ② | ③ | ④ |
| 3 | I make-up my mind quickly. | ① | ② | ③ | ④ |
| 4 | I am happy-go-lucky. | ① | ② | ③ | ④ |
| 5 | I don't "pay attention." | ① | ② | ③ | ④ |
| 6 | I have "racing" thoughts. | ① | ② | ③ | ④ |
| 7 | I plan trips well ahead of time. | ① | ② | ③ | ④ |
| 8 | I am self controlled. | ① | ② | ③ | ④ |
| 9 | I concentrate easily. | ① | ② | ③ | ④ |
| 10 | I save regularly. | ① | ② | ③ | ④ |
| 11 | I "squirm" at plays or lectures. | ① | ② | ③ | ④ |
| 12 | I am a careful thinker. | ① | ② | ③ | ④ |
| 13 | I plan for job security. | ① | ② | ③ | ④ |
| 14 | I say things without thinking. | ① | ② | ③ | ④ |
| 15 | I like to think about complex problems. | ① | ② | ③ | ④ |
| 16 | I change jobs. | ① | ② | ③ | ④ |
| 17 | I act "on impulse." | ① | ② | ③ | ④ |
| 18 | I get easily bored when solving thought problems. | ① | ② | ③ | ④ |
| 19 | I act on the spur of the moment. | ① | ② | ③ | ④ |
| 20 | I am a steady thinker. | ① | ② | ③ | ④ |
| 21 | I change residences. | ① | ② | ③ | ④ |
| 22 | I buy things on impulse. | ① | ② | ③ | ④ |
| 23 | I can only think about one thing at a time. | ① | ② | ③ | ④ |
| 24 | I change hobbies. | ① | ② | ③ | ④ |
| 25 | I spend or charge more than I earn. | ① | ② | ③ | ④ |
| 26 | I often have extraneous thoughts when thinking. | ① | ② | ③ | ④ |
| 27 | I am more interested in the present than the future. | ① | ② | ③ | ④ |
| 28 | I am restless at the theater or lectures. | ① | ② | ③ | ④ |
| 29 | I like puzzles. | ① | ② | ③ | ④ |
| 30 | I am future oriented. | ① | ② | ③ | ④ |

(Patton et al., 1995)

# ii Tridimensional Personality Questionnaire

**True/False Statements**

1. I usually am confident that everything will go well, even in situations that worry most people
2. I often try new things just for fun or thrills, even if most people think it is a waste of time
3. I like to discuss my experiences and feelings openly with friends instead of keeping them to myself
4. When nothing new is happening, I usually start looking for something that is thrilling or exciting
5. Usually I am more worried than most people that something might go wrong in the future
6. I don't mind discussing my personal problems with people whom I have known briefly or slightly
7. I would like to have warm and close friends with me most of the time
8. I nearly always stay relaxed and carefree', even when nearly everyone else is fearful
9. I usually demand very good practical reasons before I am willing to change my old ways of doing things
10. I often have to stop what I am doing because I start worrying about what might go wrong
11. I hate to change the way I do things. even if many people tell me there is anew and better way to do it
12. My friends find it hard to know my feelings because I seldom tell them about my private thoughts
13. I like it when people can do whatever they want without strict rules and regulations
14. I often stop what I am doing because I get worried even when my friends tell me everything is going well
15. It wouldn't bother me to be alone all the time
16. I like to be very organized and set up rules for people whenever I can
17. I usually do things my own way - rather than giving in to the wishes of other people
18. I usually feel tense and worried when I have to do something new and unfamiliar.
19. I often feel tense and worried in unfamiliar situations, even when others feel there is little to worry about.
20. Other people often think that I am too independent because I won't do what they want.
21. Even when most people feel it is not important, I often insist on things being done in a strict and orderly way.
22. I often do things based on how I feel at the moment without thinking about how they were done in the past.
23. I often feel tense and worried in unfamiliar situations, even when others feel there is no danger at all
24. I often break rules and regulations when I think I can get away with it.
25. I don't care very much whether other people like me or the way I do things.
26. I usually stay calm and secure in situations that most people find physically dangerous.
27. I feel it is more important to be sympathetic and understanding of other people than to be practical and tough-rninded
28. I lose my temper more quickly than most people.
29. I am usually confident that I can easily do things that most people would consider dangerous (such as driving an automobile fast on a wet or icy road).
30. I often react so strongly to unexpected 'news that say or do things that I regret.
31. People find it easy to come to me for help, sympathy, and warm understanding
32. I am much more reserved and controlled than most people.
33. When I have to meet a group of strangers. L am more shy than most people
34. 1 am strongly moved by sentimental appeals (like when asked to help crippled children)
35. I almost never get so excited that I lose control of myself
36. I have a reputation as someone who is very practical and does not act on emotion
37. I often avoid meeting strangers because I lack confidence with people I do not know
38. I usually stay away from social situations where I would have to meet strangers, even if I am assured that they will be friendly
39. I usually push myself harder than most people do because I want to do as well as I possibly can
40. I am slower than most people to get excited about new ideas and activities
41. I often push myself to the point of exhaustion or try to do more than I really can.
42. I would probably stay relaxed and outgoing when meeting a group of strangers, even if I were told they were unfriendly
43. It is difficult for me to keep the same interests for a long time because my attention often shifts to something else
44. I think I would stay confident and relaxed when meeting strangers, even if I were told they were angry at me.
45. I could probably accomplish more than do but I don't see the point in pushing myself harder than is necessary to get by
46. I like to think about things for a long time before I make a decision.
47. Most of the time I would prefer to do something a little risky (like riding in a fast automobile over steep hills and sharp turns) rather than having to stay quiet and inactive for a few hours
48. I often follow my instincts, hunches, or intuition without thinking through all the details
49. I try to do as little work as possible even when other people expect more of me
50. I often have to change my decisions because I had a wrong hunch or mistaken first impression
51. Most of the time I would prefer to do something risky (like hang-gliding or parachute jumping) rather than having to stay quiet and inactive for a few hours
52. I am satisfied with my accomplishments, and have little desire to do better

53. I see no point in continuing to work on something unless there is a good chance of success
54. I have less energy and get tired more quickly than most people
55. I usually think about all the facts in detail before I make a decision
56. I nearly always think about all the facts in detail before I make a decision, even when other people demand a quick decision
57. I often need naps or extra rest periods because I get tired so easily
58. I don't go out of my way to please other people
59. I am more energetic and tire less quickly than most people
60. I am usually able to get other people to believe me, even when I know what I am saying is exaggerated or untrue
61. I find it upsetting when other people don't give me the support I expect from them
62. I can usually do a good job of stretching the truth to tell a funnier story or to play a joke on someone.
63. I usually can stay "on the go." all day without having to push myself.
64. I am usually more upset than most people by the loss of a close friend.
65. I have trouble telling a lie, even when it is meant to spare someone else's feelings
66. I am better at saving money than most people.
67. Even after there are problems in a friendship, I nearly always try to keep it going anyway
68. I recover more slowly than most people from minor illnesses or stress.
69. I need much extra rest, support or reassurance to recover from minor illnesses or stress
70. I often spend money until I run out of cash or get into debt from using too much credit
71. I seldom get upset when I don't receive the recognition I deserve.
72. Because I so often spend too much money on impulse, it is hard for me to save money - even for special plans like a vacation.
73. It is extremely difficult for me to adjust to changes in my usual way of doing things because I get so tense, tired, or worried
74. If I am feeling upset, I usually feel better around friends than when left alone
75. I usually feel much more confident and energetic than most people, even after minor illnesses or stress
76. Some people think I am too stingy or tight with my money
77. I often keep trying the same thing over and over again, even when I have not had much success in a long time
78. It is hard for me to enjoy spending money on myself, even when I have saved plenty of money
79. I seldom let myself get upset or frustrated: when things don't work out, I simply move on to other activities
80. I recover more quickly than most people from minor illnesses or stress
81. I hate to make decisions based only on my first impressions
82. I think I will have very good luck in the future
83. I am often moved deeply by a fine speech or poetry
84. If I am embarrassed or humiliated, I get over it very quickly
85. I like tried and trusted ways of doing things much better than trying new and improved ways
86. I like to keep my problems to myself
87. I enjoy saving money more than spending it on entertainment or thrills
88. Even when I am with friends, I prefer not to open up very much
89. I feel very confident and sure of myself in almost all social situations
90. I usually like to stay cool and detached from other people
91. I never worry about terrible things that might happen in the future
92. I am more hard-working than most people
93. In conversations I am much better as a listener than as a talker
94. I like to please other people as much as I can
95. Regardless of any temporary problem that I have to overcome, I always think it will turn out well
96. I like to stay at home better than to travel or explore new places
97. I am usually so determined that I continue to work long after other people have given up
98. I usually have good luck in whatever I try to do
99. I like to play close attention to details in everything I do
100. It is easy for me to organize my thoughts while talking to someone

(Cloninger, 1987)